Pharmacist Input into Patients' Self-reporting of Adverse Drug Reactions

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TEXT BOUND CLOSE TO THE SPINE IN THE ORIGINAL THESIS

Abstract

Adverse drug reactions (ADRs) are common and should be reported to the CSM, particularly for newly marketed drugs. There is under-reporting of ADRs by doctors. Involving the patient in self-reporting, particularly when initiated by pharmacists is feasible and could help to improve reporting rates. This study investigated a comprehensive checklist questionnaire listed symptoms in all body systems to facilitate patient self-reporting using both established and new 'black triangle' centrally-acting drugs. Symptoms reported were compared to their documentation in medical notes and for new drugs to reports from other sources. A novel classification system for ADRs was developed to take account of the minimal data available and used to evaluate the potential accuracy of symptom attribution by patients. An external comparison of a sample of symptom classifications by an ADR expert was also obtained. The questionnaire was sent to 464 patients prescribed carbamazepine, sodium valproate, trazodone, doxepin and co-proxamol from three participating medical practices in a pilot study. Subsequently, it was sent to all patients (n=2307) prescribed tramadol, fentanyl patch, venlafaxine, nefazodone, citalopram, moclobemide, gabapentin, lamotrigine and topiramate from 79 participating medical practices in Grampian during January-March 1997.

The overall response rates were 44.6% (n=207) for the pilot study and 36.3% (n=837) for the main study. The most frequently reported symptoms were: drowsiness for carbamazepine, unusual tiredness for sodium valproate, constipation for co-proxamol, dry mouth for trazodone, doxepin, tramadol, venlafaxine, nefazodone, moclobemide and citalopram, weight gain for gabapentin, loss of memory for lamotrigine, weight loss for topiramate and constipation for fentanyl patch. Overall only 22.4% (522 / 2330) of symptoms reported by patients were recorded by GPs in the 310 medical notes

accessed. In general, common symptoms were reported more frequently by patients than in CSM reports and PEM data. Patients tended to report minor and known ADRs which bothered them, while CSM and PEM reports received were of more severe ADRs. Respondents were more likely to report symptoms (6040 / 8630, 70%) potentially caused by the study drugs than those not to be caused by the study drugs. Moderate agreement (Kappa = 0.4-0.5) was found between expert and researcher classifications of symptom causality. It is suggested that interpretation by pharmacists of patient self-reporting using the checklist questionnaire could result in much higher ADR reporting rates, in particular for new drugs.

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Chapter 1

Review of Literature

1.1 Introduction

A number of patients experience undesirable effects from drugs despite taking them as directed (Einarson, 1993). Concern has increased about adverse drug reactions (ADRs) since thalidomide-induced phocomelia was first mentioned in the Lancet of 2nd December 1961 (Stephen, 1992). This drug had been prescribed as a safe hypnotic during pregnancy. Following this tragic event, several countries established agencies concerned with drug safety including the Committee on Safety of Drugs in the United Kingdom (UK) to identify and prevent illness caused by drugs (Davies, 1991). The practolol disaster which caused oculomucocutaneous syndrome in 1975 later reinforced this need since it was claimed that side effects of practolol had been discovered much earlier in clinical trials (Stephen, 1992). In addition, during the 1970s and 1980s there had been a series of major ADRs such as subacute myelo-optic-neuropathy caused by clioquinol, deaths from liver diseases caused by ticrynafen and benoxaprofen, anaphylactoid reactions caused by zomepirac and renal failure caused by suprofen. These also had led academic investigators, the pharmaceutical industries and the Food and Drug Administration (FDA) of the United States (US) to develop new methods for studying drug effects in large populations (Strom, 1994a).

1.1.1 Limitations of pre-marketing studies

Clinical trials, required as part of the process of drug approval and labelling, are the primary source of information about new drugs. Although these studies confirm that a

drug is efficacious and not harmful, they frequently fail to provide the information which is necessary in therapeutic decision-making or to identify all ADRs (Ray et al., 1993). Generally, clinical trials have limited sample sizes and usually last no longer than three years. The numbers of subjects who are exposed to a drug should be between 500 and 3000 in order to be 95% certain of detecting ADRs that occur in 1-6 persons per thousand of exposed individuals (Strom, 1994a). Therefore, ADRs which occur less commonly than this are less likely to be found. Thus infrequent or rare serious reactions (1 in 10,000 - 1 in 100,000), as well as delayed reactions which result from long-term administration, cannot be detected in these pre-marketing studies (O' Donnell, 1994). Furthermore, clinical trials generally seek subjects who provide homogenous data as much as possible in order to decrease unexplained variability in outcome variables and increase the probability of detecting a difference between study groups. For these reasons, patients with other illnesses or those taking other drugs concomitantly are often excluded (Strom, 1994a). Another limitation is the age of patients included in trials e.g., the elderly are often excluded, no children are included, despite the finding that susceptibility to ADRs increases in these patients. Moore et al. (1998a) reported that overall 51% of serious ADRs of marketed drugs had not been detected prior to approval.

These limitations have created a need for comprehensive, efficient and cost-effective systems to establish post-marketing drug surveillance that confirms or extends the data from pre-marketing studies and to determine a wider range of ADRs in the general population (Generali et al., 1995; Timm et al., 1995).

1.1.2 Morbidity and mortality associated with ADRs

Several post-marketing surveillance studies have reported that ADRs were either a major cause or an important factor leading to hospital admissions. ADRs related to hospitalisation have been widely investigated. Seeger et al. (1996) summarised that ADRs which were reported to cause admission or occur during admission varied from an estimated low of 0.66% to a high of 36.4% of hospital admissions. Studies in hospitalised patients, most of which used ADRs as the outcome, also showed that injuries due to drugs were common in these patients, although the true incidence was controversial and varied considerably from 1.5% to 35% (Walker and Wynne, 1994; Bates et al., 1995). Clyne et al. (1992) concluded that the proportion of hospitalised patients who had experienced ADRs ranged from 10% to 20%. ADRs which were related to hospital admissions accounted for 3-6% and the mortality rates may be up to 0.1%. The Boston Collaborative Drug Surveillance Project estimated that approximately 30% of hospitalised patients experienced ADRs and that 3 - 28% of all hospital admissions were related to ADRs (Classen et al., 1997). In the community the incidence of ADRs ranged from 2.6% to 41% (Asscher et al., 1995). The diversity of these findings could be attributed to many factors such as differences in methods, definitions used to identify ADRs, probability ratings (i.e. inclusion or exclusion of definite, probable and possible drug reactions), clinical settings, intensity of data collection or observation and patterns of prescribing practices (Walker and Wynne, 1994; Seeger et al., 1996; Nelson et al., 1996; Asscher et al., 1995: Hallas et al., 1990).

Lazorou et al. (1998) studied the incidence of serious ADRs from 39 prospective studies in US hospitals by retrieving data from four electronic databases during 1966-1996. The study found the overall incidence of ADRs was 6.7% and of fatal ADRs was

0.32% of hospitalised patients. These could account for up to 140,000 deaths annually in the USA, making ADRs the fourth to sixth leading cause of death. A similar study retrieving data from databases between 1966 and 1989, with median sample sizes of 714, was conducted by Einarson (1993). This study showed that the prevalence of reported admissions resulting from ADRs was 5.1%. Of these, 3.7% of patients admitted due to ADRs died. A study demonstrated that 4% of the patients hospitalised in New York in 1984 suffered an injury associated with medical treatments. The most common types of adverse events found were complications related to drugs, representing a fifth of all adverse events (Bates et al., 1993; May, 1997).

McKenney and Harrison (1976) studied 216 patients admitted to a general 100-bed ward in a large teaching hospital and showed that 11.1% of patients experienced an ADR associated with hospital admissions and ADRs caused hospital admission in 7.9% of the patients. A prospective study of 452 patients admitted to the intensive care unit or internal medicine service of a university-affiliated hospital concluded that 16.2% of patients were admitted due to drug-related morbidity, of which 32.9% had an adverse reaction (Nelson and Talbert, 1996). In another study, 333 patients in a medical ward were monitored for drug events as a cause of hospitalisation. It was recognised that drug induced hospitalisation accounted for 10.8% of all admissions. Of these, 8.1% were ADRs and 2.4% were definitely avoidable (Hallas et al., 1990). A prospective study in an acute psychiatric ward involving 321 patients over a period of 17 months found ADRs to be the main cause of hospitalisation in 7.5% of patients (Hermesh et al., 1985).

A recent study carried out by Moore et al. (1998b) in 329 patients admitted to an internal medicine ward in France over six months, reported 3% of the admissions were related to ADRs and 6.6% of hospitalised patients had significant ADRs.

Cunningham et al. (1997) carried out a study in elderly patients admitted to Tayside hospitals in the UK over a nine-month period and found 5.9% of admissions were secondary to ADRs. A similar, more recent study undertaken in Aberdeen over an eight-month period showed that the most common category of drug related problems was ADRs and ADR-induced hospitalisation represented 4% of elderly admissions (Pongwecharak, 1998). Fenner and Whittington (1994) examined retrospectively the record for Coroner's Inquests in a district at Birmingham during 1986-1991 to determine the number of deaths due to ADRs. There were 36 deaths related to ADRs from the total of 3277 cases which had come to inquest.

1.1.3 Cost and preventability of ADRs

Prolonged hospitalisation and increased morbidity and mortality resulting from ADRs lead to increased health care expenditures. In the USA, ADRs add billions of dollars to annual heath care costs (Mahoney et al., 1991). One seventh of all hospital days were reported to be devoted to the care of drug toxicity at an estimated cost of $ 3 billion annually (O' Donnell, 1994).

A matched case-control study revealed that the extra length of hospital stay and the excess cost of hospitalisation attributable to an adverse drug event (ADE) were 1.74 days and $ 2013, respectively. The increased risk of death among patients experiencing an ADE was 1.88 (Classen et al., 1997). A study by Bates et al. (1997) including 4018 admissions to a 700-bed teaching hospital was performed to assess the additional resource utilisation related to ADEs. It was estimated that the post-event costs attributable to each individual ADE was $ 2595 for all ADEs and $ 4685 for preventable ADEs. The annual costs relevant to all ADEs and preventable ADEs for this hospital were $ 5.6 million and $ 2.8 million, respectively. Johnson and Bootman

(1995) also evaluated health care costs associated with unresolved or unrecognised drug-related problems in the US ambulatory care population and estimated that the cost ranged from $ 30.1 billion to $ 136.8 billion. Moore et al. (1998b) assessed the frequency and cost of ADRs causing or prolonging hospitalisation in 329 patients admitted to an internal medicine ward and concluded that ADR-related excess hospital stay was 318 days. This accounted for 8.6% of all hospital days. Between 5% and 9% of hospital costs involved ADRs. Seventy seven percent of the ADRs which patients experienced were associated with the pharmacological properties of the drugs and therefore were presumably avoidable.

Furthermore, Clyne et al. (1992) in prospective and retrospective studies found that community-acquired ADRs represented 42% of the total 541 reported ADRs. The majority (87%, $ 482,627) of expense was required to treat ADRs that occurred in the community rather than in the hospital. Conversely, hospital-acquired ADRs accounted for only 13% of the total costs.

Most ADRs are dose-dependent, related to the pharmacological characteristics of a drug and predictable. Many patients suffer injuries as a result of such occurrences, which are frequently preventable. Pearson et al. (1994) concluded that 30-80% of ADRs were preventable. A prospective cohort study evaluated preventability of ADEs in 2967 patient-days in seven units of an urban tertiary hospital. It was revealed that 27 incidents were judged ADEs. Of these, 56% were judged definitely or probably preventable (Bates et al., 1993). A further prospective cohort study investigated ADEs in 4031 adult admissions to 11 units in two hospitals over a six-month period and concluded that 42% of the life-threatening and serious ADEs, and 18% of significant ADEs were preventable (Bates et al., 1995).

Cunningham et al. (1997) also showed that ADRs were the main category of drug-related problems (DRPs) primarily responsible for patient admissions, accounting for 64.8% of the admissions related to DRPs. Over 66% of admissions due to ADRs of NSAIDs were considered to be definitely preventable and a further 26.7% were possibly preventable. Additionally, Pearson et al. (1994) carried out a study in a community hospital by reviewing all ADRs reported during a six-month period. Of the 203 reported ADRs, 19% were identified as preventable. The percentage of the preventable ADRs in this study seemed to be low because their ADR definition excluded therapeutic failure and data were collected from a concurrent ADR reporting system rather than a retrospective chart review method. Nelson and Talbert (1996) prospectively reviewed the medical charts of 452 patients admitted consecutively to an intensive care unit or internal medicine service. The result was that approximately half of drug-related hospital admissions were definitely avoidable.

These studies show that increasing awareness of ADRs and their early detection could result in fewer admissions and reduced costs.

1.2 Definitions and classification of ADRs

The World Heath Organisation (WHO) proposed the definition of an Adverse Drug Reaction (ADR) as 'any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy'. This definition, which is one of the most commonly cited, excludes therapeutic failures, intentional and accidental poisoning (i.e. overdose), and drug abuse. Furthermore, it does not include adverse events caused by errors in drug administration or non-compliance (Lazorou et

al., 1998). However, other definitions broaden the scope of ADRs by including complications caused by misuse (Leape, 1995).

Another commonly cited definition is that of Karch and Lasagna (1975). They defined an ADR as 'any response to a drug which is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose'.

The European Union also defined ADRs in an article of the Council Directive, one of the two texts containing new regulations published in the Official Journal of the European Communities. This definition was 'a reaction which is harmful and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function' (Danan, 1994), thus is similar to the WHO definition.

Dahlgren (1997) used a definition of ADRs as 'any non-preventable adverse experience associated with the use of a drug, including any injury, toxicity, or sensitivity'. A much simpler definition of ADR is described as 'unwanted or unintended effects of a medicine which occur during its proper use' (Asscher et al., 1995). Some include drug interactions to broaden the definition of ADR (May, 1997), while other definitions include statements relating to causality. For example, Kramer et al. (1979) defined an ADR as 'an undesirable clinical manifestation consequent to and caused by the administration of a given drug'. The International Federation of Pharmaceutical Manufacturers' Association (IFPMA) also recommends 'an ADR is defined as an adverse event which is causally related to the drug'. The United States Food and Drug Administration definition however opposes this. It states that an ADR is 'any experience associated with the use of a drug whether or not considered drug-related

and includes any side effects, injury, toxicity or sensitivity reaction or significant failure of expected pharmacological action' (Stephen, 1992).

Conventionally, ADRs are classified into overdosage, intolerance, side effects, secondary effects, idiosyncrasy, hypersensitivity reactions and drug interaction. Logically, ADRs can be divided into those that arise from the normal pharmacological properties of a drug and those that represent an abnormal and novel response to a drug. Such divisions can be classified into two types (A and B) (Rawlins and Thompson, 1977). Type A (Augmented) reactions are normal pharmacological effects of the drug exaggerated to produce undesirable results. These reactions cause 70% to 80% of ADRs. Therefore, they are usually predictable and probably preventable. Examples of this type of reaction would be postural hypotension from antihypertensive drugs, drowsiness induced by diazepam or phenobarbital, warfarin causing bruising, dry mouth and other anticholinergic effects due to antihistamines or tricyclic antidepressants. Moreover, the reactions are often dose-dependent and the incidence of morbidity in the population is fairly high, but their fatal effect is low. Type B (Bizarre) reactions are unusual effects that are unrelated to or unexpected from the known pharmacological action of the drug. These reactions are unpredictable, unavoidable and may or may not be dose-dependent. They are particularly dangerous. The mortality rate is high but the total incidence is significantly low. Examples of this type of reaction are agranulocytosis secondary to chloramphenicol, allergic-hypersensitivity reactions from antibiotics and anaphylactic reactions, which is one of the most serious and potentially life-threatening reactions caused by penicillins. The terms 'idiosyncratic' or 'allergic' reactions are used widely as a synonym of type B reactions (May, 1997; O' Donnell, 1994).

Recently, Wills and Brown (1999) discussed the limitations of the previous classification suggesting that it was sometimes difficult to decide whether certain reactions were type A or type B, for example, cancers in patients taking immunosuppressants, injection site reactions, drug interactions and therapeutic failure. Consequently, these workers proposed a new classification of adverse drug reactions into 9 categories, i.e. type A (augmented reactions), type B (bugs reactions), type C (chemical reactions), type D (delivery reactions), type E (exit reactions), type F (familial reactions), type G (genetotoxicity reactions), type H (hypersensitivity reactions) and type U (unspecified reactions). Lee (1999) however commented that this new classification may still have problems in use. This classification is not in general use and may not become widespread since it lacks simplicity.

1.3 Methods for detecting ADRs

Post-marketing surveillance (PMS) is the study of drug use and drug effects after marketing, although it is sometimes applied only to studies undertaken after drug marketing which systematically screen for ADRs (Strom, 1994b). IFPMA gave the definition of PMS as all methods, including spontaneous reporting, used to define more precisely the benefits and risks of drugs under normal prescribing circumstances. Inman (1986) defined PMS as a term often used to describe techniques to detect or measure the incidence of ADRs, while Stephen (1992) viewed PMS as the systematic detection and evaluation of adverse events occurring in association with drugs or biologics under customary conditions of use in ordinary medical practice. However, the term is commonly used in its wider sense by including all kinds of schemes for generating or testing hypotheses about drug events.

The aims of PMS are to detect and identify ADRs as early as possible, particularly severe and unexpected reactions, to record the frequency and incidence of ADRs as well as possible, and to analyse the collected data in order to use it to take any regulatory action which might be needed to prevent ADRs in the future (Venulet and Ham, 1996; Saine, 1992).

There are two main types of PMS used to monitor ADRs, descriptive studies and analytical studies, based on whether or not a hypothesis is being sought or tested.

1.3.1 Descriptive studies

These studies describe events related to ADRs in various populations and do not establish any causal relationship. As they do not have a control group, these studies are hypothesis-seeking.

1.3.1.1 Spontaneous reporting

The spontaneous reporting system (SRS) for ADRs is dependent on voluntary collaboration by doctors working in hospital or in medical practice as well as other health professionals. Their ADR reports are sent to drug regulatory authorities or organisations at the national level to collect, sort and examine serious events associated with drugs. The spontaneous reporting serves as an early warning system for serious and unexpected ADRs. As this scheme is voluntary, the number of ADRs reported are only a small fraction of the actual number occurring in the population, so the rate of underreporting is high, up to 85 - 98% of doctors, depending on the country. The reporting rates in 14 Melbourne Teaching hospitals during 1991 varied from 0.02% to 0.72% which were much lower than those reported from an intensive hospital

monitoring scheme (Raymond, 1994). Also, a relatively small number of doctors were responsible for a disproportionately high number of the total reports (Spencer, 1995; Venulet and Ham, 1996). SRS provides the best means of rapidly identifying new and rare ADRs. A large amount of data can be collected, numerous drugs can be studied and a wide variety of organ systems can be observed at relatively low administrative expenditures. However, such schemes are of limited use in quantifying the frequency of drug reactions due to the lack of completeness of ADRs reported (the numerator) and the total number of patients prescribed the drug (the denominator). Consequently, they cannot provide a reliable incidence of ADRs. They may have bias resulting from publicity and also have limitations in assessing the relative risk of drugs within the same therapeutic group, in identifying delayed ADRs and in the validity of individual reports (Anonymous, 1977; Inman, 1986).

SRS have now been developed around the world, such as the Yellow Card scheme of the CSM in the UK and the MedWatch scheme of the FDA in the USA. The national reports are subsequently sent to the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, which is now receiving almost 200,000 reports per year (Meyboom et al., 1997a).

In the USA, the MedWatch programme started in June 1993 and is designed to promote and facilitate voluntary reporting by health professionals of serious ADRs. It was developed because the FDA revealed that as many as 50% of physicians were not even aware that the FDA had a reporting system for ADRs. The FDA emphasised that it was unnecessary to prove causality, so physicians should submit reports even if there was only a suspicion of a serious event related to drugs (Gruchalla, 1995; Kennedy et al., 1993).

Likewise, there is a European pharmacovigilance system called Rapid Alert Scheme, which was introduced in late 1988 to improve communication on important drug safety issues. The member states are required to inform other EC members and the Commission by fax of any drug safety issue that is likely to lead to significant licensing action (Wood, 1992).

1.3.1.2 Cohort studies without control groups

This kind of the study aims to identify ADRs as quickly as possible. Several thousand patients treated with the drugs studied are monitored by systematic observation under normal conditions including assessment of ADRs. In 1977, there were a number of studies using this method, for example, Register release and Monitored release. The Register release collected data from a predetermined number of patients registered for this purpose and analysed this before the product was finally licensed. There were no other patients taking the drug during the period of study (Venulet and Ham, 1996). The Monitor release scheme studied licensed drugs by asking pharmacists to keep a record for a certain period of all patients coming to them and by periodically checking back with doctors whether they noticed any ADRs in these patients (Stephen, 1992; Wilson, 1977). However, these methods mainly depended on the willingness of participating doctors and pharmacists.

1.3.2 Analytical studies

These studies determine causal relationships or associations between the study drug and the reactions which have occurred. They can be used for hypothesis testing since they have a concurrent control group.

1.3.2.1 Case-control studies

Case-control studies are studies that compare cases with a disease or event to controls without the disease or event and look for differences in antecedent exposure. These studies are frequently used in testing hypothesis about drug-related disease. Cases are sought in which a particular adverse event occurred. For these patients, those receiving the drug are counted. The control group consists of patients in whom the adverse event did not occur. Subsequently, case and control are compared on the basis of frequency rate as well as the relative risk. This method can detect uncommon or rare ADRs and can be undertaken quickly and easily at relatively low cost. However, it may lead to a number of biases and appropriate control groups are sometimes difficult to select. Examples of the type of case-control studies include the association between venous thromboembolism and oestrogen therapy in postmenopausal women and pancreatitis associated with thiazide diuretics (Grasela, 1996; Lawson and Beard, 1992; Strom, 1994c).

1.3.2.2 Cohort studies (Controlled)

Cohort studies are studies which identify subsets of a defined population and follow them over time, looking for differences in their outcome. A group of patients taking the study drugs are compared with patients who are not taking them or are taking other drugs. The studies can be performed either prospectively or retrospectively. Cohort studies select subjects on the basis of the presence or absence of an exposure to a study drug, while case-control studies select subjects into the study on the basis of the presence and absence of a disease or event. This type of study not only requires a prolonged period of time, especially for delayed ADRs if undertaken prospectively, but is also more expensive than case-control studies. Cohort studies however have major

advantages over case-control studies in that control groups are easier to select, bias is less likely to occur and more reliable data is obtained. They are particularly useful in PMS of newly marketed drugs, even though they need large sample sizes to study uncommon ADRs (Morse et al., 1986; Strom, 1994c; Venulet and Ham, 1996). Several cohort studies have been conducted. A classic example is the study of a total of 10000 patients taking cimetidine in the UK who were followed up for an 18-month period in 1981 (Stephen, 1992). Prescription-event monitoring (PEM) is one example of drug-based or outpatient cohort studies. It identifies 10,000-20,000 patients from photocopies of prescriptions provided by the Prescription Pricing Authority (PPA) (Waller, 1991). (see section 1.4.2)

1.3.2.3 Population-based studies or Record- linkage studies

This method is probably the only realistic approach to carrying out screening procedures which require very large sample sizes (Carson et al., 1994). The availability of computers has led to record-linkage schemes retrieving information from many sources including hospitals, general practices, national registers, etc. Studies can be limited to hospitalised patients or may cover a relatively large proportion of the total population.

A. Hospital-based population studies

These studies can also be called Intensive hospital monitoring. This method provides standardised information on a database on all patients, therefore, data are not only reliable and complete, but also follow up can be easily undertaken to investigate ADRs extensively. Therefore incidence rates can be calculated. Data collected can also prove causality and the role of additional factors, however, the costs to achieve a

satisfactory number of cases are high and the period of observation is limited as this method is performed in hospitalised patients. Examples of this method are the Boston Collaborative Drug Surveillance Program and the Aberdeen-Dundee System (Inman, 1986; Venulet and Ham, 1996). Additionally, Bates (1998) proposed that these studies using computer surveillance be used to assist in identifying ADRs in hospitals as a much more efficient approach than a chart review method.

An example of this is the use of automatic signals from laboratory data in hospitalised patients followed by retrospective chart review of every third patient (Tegeder et al., 1999). This study found that 18 of 98 patients experienced probable ADRs and only one third of these were recognised by the attending physicians. A comparison between ADR monitoring involving prospective surveillance and retrospective reviews of medical records was undertaken for an entire hospital. The prospective programme included chart review for all patients with an order for drugs that might be used to treat an ADR and with elevated serum concentrations of selected drugs. The retrospective programme was conducted by reviewing all charts with E-codes and diagnosis codes that might indicate reactions to a drug for the same period to confirm the occurrence of ADRs. It was found that 37% of ADRs were identified by prospective monitoring and 68% by retrospective reviews while 5% were identified by both methods. This results contrasted to a study of Schumock et al. which reported that a medical record-based retrospective reporting system was less sensitive than a pharmacy-based prospective reporting system (Madsen, 1993).

B. General population-based studies

Data from these studies can apply to an identifiable population, all of whose medical care is included in a database, regardless of the provider. This allows the

determination of incidence rates of ADRs in the light of complete information about medical care given to patients. The advantages of these studies are; relatively low costs and time involvement for large sample sizes, suitability for uncommon or rare ADRs, the possibility of follow up for long-term trends and the ease of obtaining sufficient data. However, these studies may not be representative of the population at large, there is often no control of confounding factors, and the validity of the data is less certain than in hospital-based settings. There are methods of improving the data, such as using drugs and procedures as markers of disease and obtaining primary medical records.

Examples of this type of study include COMPASS (Computerised On-line Medicaid Pharmaceutical Analysis and Surveillance), MEMO (The Medicine Evaluation and Monitoring Unit) in Dundee, Scotland and The Oxford Record-linkage, England (Morse et al., 1986; Lawson, 1991; Strom, 1994d; Stephen, 1992).

1.4 ADR monitoring systems in the UK

1.4.1 Yellow Card Scheme

The UK spontaneous reporting system has been operational since 1964 and is known as the Yellow Card Scheme. It is organised by the CSM, a committee of the Medicines Control Agency (MCA) which has specific responsibilities for promoting the collection and investigation of information related to adverse reactions. The MCA is the organisation which is responsible for licencing of medicines in the UK, monitoring the safety, investigating possible hazards and taking action to minimize the risks to users (Waller et al., 1996; Mann, 1992). It is widely recognised that this scheme plays an important role in identifying and assessing drug toxicity. The system depends on the

voluntary reporting of suspected drug reactions by health professionals either directly to the CSM or indirectly through drug companies (Mann, 1992; Bateman et al., 1991; Rawlins, 1988; Wilson, 1977). The drug manufacturers are required to report all ADRs to the MCA, especially serious and unexpected ADRs, within 15 days. The doctors are asked to report all events including the minor ones with new drugs marked with a black triangle in the data Sheet Compendium and the British National Formulary (BNF), and also to report serious reactions, even well-known ADRs, with the older drugs. The reports are received by the subcommittee on Safety, Efficacy, and Adverse Reactions, which collects and assesses each report, determines epidemiological issues, and when warranted disseminates information to doctors and pharmacists (Scott et al., 1988; Anonymous, 1980).

To date, more than 300,000 UK reports of suspected ADRs have been received. The reports are held on a computer database called ADROIT (Adverse Drug Reactions On-line Information Tracking), which was introduced in 1991, by combining images processing with a relational data base. Approximately 100 ADR reports are received daily and entering data into this database is prioritised by the seriousness of reactions in order to provide signal generation of previously unrecognised ADRs or new information on established ADRs which might need action. Likewise, reaction profiles compare the pattern of reactions to a drug in relation to the pattern of reactions caused by other therapeutically related drugs. A number of data output programmes have been developed on ADROIT. These include alert programmes which allow new ADRs or changing patterns of reactions to be picked up more readily and programmes screening the database regularly for entirely new reaction associations or evidence of new reactions. In addition, there are programmes relating ADRs to drug usage which give estimates of changing reporting rates either for individual drugs or therapeutic groups of drugs (Wood and Coulson, 1993; Waller et al., 1996).

Since 1975, the CSM has produced a drug safety information bulletin for all doctors, dentists, coroners and pharmacists practising in the UK which is known as Current Problems. The bulletin, which is issued at approximately 3-monthly intervals, aims regularly to inform and alert health professionals about important drug safety issues particularly newly-recognised, serious ADRs so that they can use drugs more safely. It also provides feedback from the spontaneous reporting system (Lawson and Beard, 1992; Waller et al., 1996).

The UK reporting scheme has successfully provided early warning of a number of ADRs, for example, extrapyramidal reactions induced by metoclopramide, blood dyscrasia induced by mianserin and gum hyperplasia induced by nifedipine (Rawlins, 1988). However, the CSM itself estimates that probably only 10% of serious adverse reactions are reported to the Committee. Rassaby and Medawar (1992) also commented that if patients are treated concomitantly with several similar drugs, it is difficult for the Yellow Card Scheme to resolve which drug was responsible for those reactions.

1.4.2 Prescription-event Monitoring (PEM)

PEM is a system of PMS established by the Drug Safety Research Unit (DSRU) at Southampton University which aims to monitor all new drugs used in general practice in England, to study a cohort of at least 10,000 patients taking the drug for up to a year, to generate hypotheses about adverse reactions, to test specific hypotheses, to measure the frequency of adverse events after exposure to a new drug and to complement the existing spontaneous reporting system (Waller, 1991). This enabled detection of ADRs by a comparison of the relative incidence of events in groups of patients receiving different drugs for similar complaints. It was suggested that the

system could feasibly detect ADRs occurring with at a frequency of 0.1% (Inman, 1981).

The system involves the retrieval of prescriptions for drugs selected for study from Prescription Pricing Authority (PPA). Prescriptions presented to pharmacists for dispensing in England are submitted to the PPA in order to reimburse the costs of the drugs. Photocopies of selected prescriptions are sent to the DSRU in Southampton in order to obtain the patients' name and address, sex, surgery code, unique doctor code together with the date of prescription. These are then processed to identify the patient, doctor and the fact that drug exposure has occurred. After a short period of time (3, 6 or 12 months), a standard questionnaire or green form is sent to the prescribers to obtain further information including data on any events that may have occurred. The green form also requests the following information; age sex, indication, start date of study drug (and stop date, if applicable, plus the reason for stopping and drug substituted) and an opinion of its efficacy. These data are then entered onto the computer and comprise the outcome data (Fleming, 1994; Waller, 1991). The analysis of PEM data is based on the comparison of the incidence of events during the first month of treatment with the incidence in subsequent months for all patients prescribed that drug. Using ad hoc rules for assessing the relative excess of events associated with taking a drug, a rate ratio of more than 3 was regarded as sufficiently large to signal a possible ADR. For example, diltiazem induced rash at the rate ratio of 4.6. However, this might be affected by various biases, such as underreporting in subsequent months and different age and sex pattern of the cohort patients. In addition, event rates for the study drug can be compared with an estimate of the background level assessed from a range of other drugs and based on patients similar to the patients taking the study drug (Andrew et al., 1996; Kubota et al., 1995).

PEM is an important development in PMS and now is an alternative national PMS system to the yellow card scheme. The strength of PEM is that it provides a means for monitoring new drugs early after launch with impeccable exposure data and reliable outcome data. Therefore, new ADRs, which represent previously unspecified reactions, can be detected. Since it is carried out retrospectively, PEM does not influence prescribing practices. However, unlike the yellow card scheme, PEM cannot detect rare ADRs except by chance and it is difficult to study ADRs of older drugs (Rawson et al., 1990; Mann, 1995; Waller, 1991). Furthermore, this system solely depends on collaboration of the general practitioners to provide essential information. During the development of PEM (1980-1984), the response rates from general practitioners were at least 70% but since 1984 the rates of returned questionnaires has often fallen below 50% (Inman and Pearce, 1993).

1.4.3 The General Practice Research Database (GPRD)

The GPRD formerly called VAMP (Value Added Medical Products) is an important source of drug usage data from general practice. It has assembled the largest database covering a large population (around 4 million patients) in which morbidity requiring treatment, referral and prescribing data are gathered routinely in general practices. It is the most important record linkage database for monitoring drug safety in the UK. Since 1993 the database has been held by the Department of Health and managed by the Office of National Statistics (ONS). The MCA can access this database for investigation and confirmation signals, monitoring the effects of regulatory action and as a source of drug usage information. It is a significantly useful database as demographic data, exposure data and outcome data are linked at source within the record of each individual patient. Thus, GRPD is capable of conducting pharmacoepidemiological studies including case control studies which can explore

hypotheses generated by the yellow card scheme and PEM (Fleming, 1994; Waller et al., 1996; Jick, 1995).

Jick et al. (1991) conducted a study to determine the extent of clinical information recorded on the computers of 58 practices covering 2491 patients taking one of three NSAIDs. Similar information was studied from manual records of letters received from hospital consultants which were kept in the general practitioners' files. It was found that 87% of the 1191 patients for whom consultants' letters contained a clinical diagnosis was present on the computer record of the general practices. Therefore, this indicated that clinical information available on the computer record of general practices is satisfactory for many clinical studies using this database.

1.4.4 The Medicines Evaluation and Monitoring Unit (MEMO) system

The MEMO Unit set up by the University of Dundee conduct record-linkage PMS studies. The facility enables hypotheses testing studies in a population of 400,000 patients in Tayside, Scotland, using a computer database. The Unit use the Community Health Index (CHI), a unique patient identifier, to track all healthcare activity in Tayside. These numbers are issued to individual patients in Scotland when they register with general practitioners. The CHI number comprises ten digits, the first six of which are the date of birth of the patient. There are two main sources of data used by MEMO which are linked by the unique CHI including information on all prescriptions dispensed and hospital data on all admissions of Tayside residents. The prescriptions and the CHI have been obtained from the Prescriptions Pricing Division (PPD) since 1989 whereas the hospitalsation data together with the CHI have been provided by Tayside Health Board since 1980. When a patient is admitted to a hospital, a computerised record known as the Scottish Morbidity Record (SMR) is

generated for every consultant episode of care including the ICD9 diagnosis code. MEMO also access other databases indexed by the CHI such as a database of all endoscopies, road accidents and other Scottish Morbidity Record databases.

Using this information, MEMO can conduct several cohort or case-control studies testing hypotheses. For example, a large cohort study to determine the risk profile of upper gastrointestinal complications related to approximately 50,000 patients taking NSAIDs and a case-control study to investigate whether upper gastrointestinal complications were associated with topically applied NSAIDs (MacDonald, 1995).

One of the strengths of MEMO is that it can validate the computerised data by comparing with the original case records in the hospital. It can also calculate the true incidence rates based on the relevant population. However, MEMO covers only 400,000 patients in the population. This sometimes makes it difficult to find proper control groups. Also, the indication for the drug prescribed is not known (Stephen, 1992; Waller et al., 1996).

1.4.5 Other monitoring methods

There are number of individual PMS studies conducted in the UK. For example, drug-oriented studies are run by an ADR team at Royal Liverpool Hospital (Stephen, 1992). A feasibility study undertaken by Drury and Hull (1981) to find out the possibility of prospectively monitoring ADRs in general practices, showed that 57% of 103 doctors recruited patients into the system and a total of 1771 prescription copies were returned by these doctors. Seventy-four percent of the follow up forms inquiring about ADRs in the subsequent periods were returned. Thus, it was considered possible to conduct a large-scale prospective monitoring for ADRs in general practices in the UK. However,

there has been no progress since then. Lumley et al. (1985) also conducted a prospective study to determine the incidence of ADRs in 24 general practices. During a four week period of study, 638 (1.7%) of 36,500 consultations were recorded as involving suspected ADRs by the participating doctors. The doctors considered 70% and 28% of these were probable ADRs and possible ADRs, respectively. Only one study by Campbell and Howie (1988) has involved patient self-reporting, conducted over two two-month periods. Patients prescribed a new drug were given a leaflet by the pharmacists in Livingston to encourage them to report any adverse reaction to their doctor. The study showed that reports of ADRs increased from six out of 576 in the control period to 11 out of 481 in the study period.

1.5 Causality assessment of ADRs

The most important problem in monitoring ADRs is whether there is a causal relationship between the drug and the unwanted reaction. The estimation of the probability that a drug caused an adverse reaction is generally dependent on clinical judgment. The lack of established causality criteria for ADRs even in case reports is well documented and experts have frequently disagreed in their assessment. Koch-Weser et al. (1977) found that three clinical pharmacologists who independently evaluated 500 ADRs reported by doctors, often disagreed with the doctors and with each other. Therefore, attempts to standardise assessment have been created through methods based on various criteria. The standardised assessment implies that the same operational logic is always applied. Commonly, the criteria of these methods are similar but their weight, gradation, specificity and number of items of information considered are different (Benichou and Danan, 1991; Venulet et al., 1980). Usually, prefixed numerical scores are attached to the answers of numerous subquestions

which then result in a cumulative value, which is interpreted into a causality category, i.e. definite, probable, possible or unlikely. The standardised assessment can improve communication between users, reproduce and validate the results, and also decrease variations in judgements of different experts (Meyboom et al., 1997b; Venulet, 1992; Emanueli and Sacchetti, 1980).

One of the initial methods established by Karch and Lasagna (1977) relies on five criteria: 1) whether the interval between drug and reaction is appropriate 2) whether it is a known reaction to the drug 3) whether the reaction is reasonably explained by the patients' clinical states or other therapies 4) dechallenge 5) rechallenge. Bergman and Wilholm (1981) also applied this method to the study of drug-related problems causing admission to a medical clinic. Kramer et al. (1979) developed an algorithm which provided a score system for six axes of decision strategy: previous general experience with the drug, alternative etiologic candidates, timing of events, drug levels and evidence of overdose, dechallenge, and rechallenge. The sum of the scores rated the ADR as definite, probable, possible, or unlikely.

However, Naranjo et al. (1981) and Busto et al. (1981) commented that application of the methods of Karch and Lasagna and Kramer et al. to routine clinical practice was limited because they were more complex and time consuming. So the authors proposed a simple method containing only ten questions as follows: temporal sequence, pattern of response, withdrawal, re-exposure, alternative causes, placebo response, drug level in body fluids or tissues, dose-response relationship, previous patient experience with the suspected drug, and confirmation by objective evidence. The total scores categorise probability of ADR into definite (≥9), probable (5-8), possible (1-4), doubtful (0). Validity testing for this method was undertaken by determining the agreement of two physicians and four pharmacists who independentl

assessed 63 randomly selected alleged ADRs. The result showed that the between-rater reliability which was represented by percent agreement ranged between 83% and 92% (Kappa=0.69-0.86). Cooper (1996) also used this probability scoring scale to assess the causality of suspected drugs studied in a rural geriatric nursing home population. The study found that 444 probable ADRs occurred in 217 of 322 residents over a four-year period. Mean probable ADRs experienced by the 217 patients was 1.9.

Venulet (1986a, 1986b) developed a checklist and assessment form for the standardised assessment of ADRs. It consists of 23 questions divided into three parts including history of present adverse reaction, patient's past adverse reaction history and monitor's experience. The form also subdivides ADR into dose-related, dose-unrelated, type I allergic, at the site of application, interaction, drug dependence, irreversible, withdrawal symptoms, foetal malformation or unclassified. These subsequently translated into five categories of causal relationship between drug and the reaction as definite, probable, possible, unlikely, or not related to suspected drug. Using this standardised assessment, the results of 1362 cases by comparing the judgement of six medical evaluators demonstrated that 62% of total cases were in complete agreement.

WHO also implemented causality assessment of suspected adverse reactions according to the presence of laboratory test abnormality, time sequence to administration of the drug, attribution by concurrent disease or other drugs, dechallenge, predication by pharmacological action, and rechallenge. In this system, there are six different degrees of causal relationship which are certain, probable/ likely, possible, unlikely, conditional/ unclassified, or unaccessible/ unclassifiable. This method aims to help in routine assessing causality of single case reports or

spontaneous reports received by the drug regulators (Meyboom, 1997b; Venulet, 1992).

Benechou and Danan (1991) designed aetiological diagnostic schemes adapted to specific and defined disorders known to be frequently induced by drugs such as liver injury, granulocytopenia, thrombocytopenia, photosensitivity reactions, renal failure, etc. These schemes were organised by consensus meetings with university experts and specialists in official pharmacovigilance on the basis of disease definition, clinical appearance and pathology, signs of severity, aetiology and diagnosis, evidence implicating a drug, chronological criteria, and management. The likelihood of a relationship for some reactions is defined in a semiquantitative way, using five different categories: incompatible, inconclusive, compatible, suggestive, or very suggestive.

Furthermore, there are computerised systems which help to overcome the complex calculations involved in causality assessment, for example, the Bayesian Adverse Reactions Diagnostic Instrument (BARDI) using a balance of probability for competing explanations which was developed by Naranjo and Lanctot (1991) and a computer programme developed for causality assessment using Venulet et al.'s method (Anonymous, 1989; Venulet, 1992).

Although these methods appear to have clear and direct criteria enabling their universal use, their application in clinical practice is not always manageable because some information such as interactions with other drugs and life style characteristics which are not considered by the method may play a decisive role in assessment. In addition, some data are often unavailable, i.e. dechallenge, rechallenge or time intervals. When the same information is assessed by several methods, the conclusions are also different or conflicting (Rogers, 1987; Venulet et al., 1986). In

fact, such methods cannot conclude that suspected drugs truly cause the reactions. They are still based on subjective decisions and can not eliminate or quantify uncertainty but only categorise ADRs into levels of probability (Bastin et al., 1984; Meyboom, 1997b).

1.6 Problems with ADR reporting systems

The ADR spontaneous reporting system (SRS) is a significant component of the postmarketing surveillance of drugs which is used nation-wide. It remains one of most important sources to identify new ADRs once a drug is on the market. The reporting system is also designed to generate signals of rare and unexpected ADRs particular in serious ADRs and creates hypotheses to be further tested in epidemiological studies. Nevertheless, the main problem of the reporting system is underreporting (Walker and Lumley, 1986; Rogers et al., 1988). The overall reporting rate is remarkably less than that expected from intensive studies. Fletcher (1995) estimated reporting rates seldom account for more than 10% of the actual ADRs that occur. The detection of new and unexpected ADRs depends considerably on the attitude, awareness and co-operation of doctors to the ADR reporting system (Bateman et al., 1992).

1.6.1 Extent of under-reporting in various countries

In France, seeking to identify the perception of drug safety by young practitioners, it was revealed that pharmacovigilance centres are still relatively unknown. The level of under-reporting of ADRs was 44%. Moreover, 66% of the residents did not know that the spontaneous reporting system was compulsory and 75% of these were unable to find the address of the regional pharmacovigilance centre (Graille et al., 1994).

In the United States, physicians are an important source for the early warning of ADRs. Direct reports from physicians sent to the FDA in 1970 were only 1% of reports received, however these accounted for 24% of all new ADRs (Scott, 1988). In 1983, only 57.6 ADRs per 1000 physicians were reported in the US. It was estimated that the reporting rates in most institutions were lower than 10-15% (Sweet and Ryan, 1994). A pilot project to determine the experience of 1167 Rhode Island physicians with fatal and severe ADRs found that less than 1% of suspected serious ADRs were reported directly to the FDA (Scott et al., 1987; Scott, 1988). In addition, a questionnaire survey of hospital pharmacy department directors at 444 randomly selected hospitals sought information on their institutions' ADR programmes. From 176 (39.6%) usable respondents, it was found that although approximately 97% of the institutions had policies for ADR reporting (there were an average of 70.5 ADRs per hospital during 1989), only 6.8 per hospital were reported to the FDA (Tyler and Nickman, 1992). Herrera et al. (1992) determined the ADR surveillance system in 61 hospitals and found larger hospitals (more than 333 beds) tended to have lower rates of reported ADRs than small ones (0.034 and 0.064 ADRs per patient days, respectively). Also, Rogers et al.(1988) revealed that less than one-fifth of 418 licensed physicians who had detected ADEs reported them to the US FDA.

In Australia, the system of ADR reporting and the rate of reporting was examined in 15 teaching hospitals. The number of reactions reported in 1991 ranged from five to 162 per hospital, with only three hospitals receiving more than 100 reports. Although all hospitals used reports from ward pharmacists, medical and nursing staff, and they had alert forms for the patient's history regarding new or previous ADRs, the rates of reporting were only 0.02 - 0.72 % (Raymond and Robertson, 1994).

In the United Kingdom, a report from the UK Medicines Control Agency suggested that underreporting was getting worse, as the number of yellow cards sent in by doctors during 1993-1994 had fallen by 17% over the previous year and only 14% of all suspected ADRs were reported in general practice (D' Arcy, 1996). Speirs et al. (1984) examined the number of doctors sending in yellow cards during 1972-1980. It was shown that of 122,000 doctors eligible to report over the period, only 16% submitted reports and a substantially decreased rate of reporting was seen among those qualified for less than five years or for more than 40 years. It had also been suggested that only 1-10% of serious reactions are reported to the CSM (Walker and Lumley, 1986). The underreporting of ADRs in 24 general practices involving 100 doctors was investigated over a four-week period by Lumley et al. (1986). There were only 13.5% out of a total of 37 ADRs which should have been reported actually submitted to the CSM. Additionally, a recent study by Martin et al. (1998) assessed the degree of underreporting of ADRs to new (black triangle) drugs in general practices through the PEM system. The results indicated that general practitioners had reported only 275 (9%) of 3045 events, which were reported as suspected ADRs on the green form of PEM, directly to the CSM. Serious unexpected and non-serious unexpected ADRs were significantly more likely to be submitted than those non-serious expected ones.

It was not only the CSM which encountered the under-reporting problem, as response rates from general practitioners to supply post-marketing data on new drugs had also been falling within the PEM system (Inman and Pearce, 1993). A comparative study between spontaneous adverse drug reaction reporting and event monitoring involving 44,000 patients contributed by 8000 general practices, demonstrated that underreporting by the spontaneous reporting system may be as high as 98% for several adverse reactions associated with drugs (Fletcher, 1991). Smith et al. (1996) retrospectively analysed data collected by a local ADR reporting scheme over a three-

year period and found that 1420 ADRs were reported with a rate of 68.7 per 1000 admission. Following the CSM guidelines for ADR reporting, 477 yellow cards should have been submitted, but only 30 (6.3%) were actually sent to the CSM and only 31 (6.5%) of these involved black triangle drugs. Furthermore, a study conducted in the Northern Region showed that up to 73% of junior doctors had never sent a yellow card report to the CSM (Bateman et al., 1992).

To summarise, the reporting rates from spontaneous reporting systems in many countries are still quite low, although the system is very useful for detecting ADRs of new drugs and rare ADRs. The reporting system is also able to alert all health professionals to be aware of unwanted drug effects. Consequently, various countries, realising the benefits, have used different methods to try and improve their reporting rates.

1.6.2 Reasons for under-reporting

Physicians have played a key role in the reporting systems. Possible reasons for the lack of success of the systems were therefore sought by a number of surveys of physicians' knowledge, attitude and utilization of the ADR reporting system. Inman and Weber (1986) described the "seven deadly sins" which inhibited reporting of ADRs in the UK as follows: 1) complacency about the safety of approved drugs 2) fear of litigation 3) guilt because of unintentional harm caused to patients 4) ambition to publish personally 5) ignorance of reporting mechanisms 6) diffidence in reporting mere suspicions, and 7) lethargy resulting in unwillingness to notify the ADRs.

Attitudes of doctors to the CSM reporting scheme were investigated by postal questionnaire sent to 500 randomly selected doctors. Of these, 57% responded to the

questionnaire and 63% of the respondents stated that they had previously reported an ADR to the CSM or to a pharmaceutical company. Reasons for under-reporting included lack of time (21%), lack of a report form when needed (21%) and the misperception that sending a report required diagnosis of an adverse reaction with absolute confidence (8%). Most doctors knew the types of reactions that the CSM requests but only one-third knew the precise meaning of the CSM's black triangle symbol. Thus, lack of understanding about the reporting scheme may lead to under-reporting (Belton et al., 1995).

The attitudes and knowledge of doctors in the North of the UK to the reporting of ADRs were assessed by postal questionnaire to which 1181 of 1600 doctors (74%) responded. There were few differences in opinion and attitude between general practitioners and consultants from high and low reporting districts. General practitioners in low reporting areas stated they wrote more prescriptions while consultants spent more time in clinical contact and junior doctors did both, all of which suggest different workloads may affect the reporting of ADRs. On questions about the CSM's black triangle scheme, all doctor groups performed poorly. Difficulty in determining the responsible drug, professional obligation, time-consuming reporting of ADRs, and complexity of the report method were the main reasons for under-reporting (Bateman et al., 1992). Other data from the Drug Safety Research Unit in Southampton revealed that there was a consistent inverse relation between the number of prescriptions and the response to requests for postmarketing information (Inman and Pearce, 1993).

A further survey was conducted by sending a questionnaire to 60 doctors at the Royal Liverpool hospital. Diffidence (39%), ignorance (37%), lethargy (13%), ambition (5%), guilt (2%), fear (2%) and complacency (2%) were the reasons of the hospital doctors

for not reporting ADRs to the CSM. Of the respondents, 34% stated that it was difficult to assess the responsible drug if patients were taking multiple drugs, while there was 30% felt difficulty in distinguishing the disease state from the reaction caused by the suspected drug (Randhawa and Smith, 1987). A retrospective study by Smith et al. (1996) analysed data collected by a local ADR reporting scheme in an acute hospital medical setting and found well-known reactions to established drugs was the main reason for the low proportion of yellow card reporting. Walker and Lumley (1986) also designed a questionnaire to obtain information about general practitioners' opinions of the yellow card scheme. Of the total of 402 GP respondents, 30% thought the scheme was unsatisfactory and 95% thought more feedback from the CSM would improve the under-reporting.

Studies in the USA also found similar reasons for under-reporting. In Rhode Island, 74% of 1,585 physicians contacted responded to a questionnaire which found that only 55% of respondents were familiar with the reporting system. They displayed a poor knowledge of and underreporting of the ADR reporting system. A lack of report forms, uncertainty about the drug which caused the reaction, don't know how to report and expectation of the reaction were identified as major impediments to reporting (Scott et al., 1987). After implementing various interventions, physicians were resurveyed in the next two years. Respondents improved their knowledge and understanding of the ADR reporting system, but lack of certainty concerning the suspected drugs was still a major problem of non-reporting (Rosenbaum et al., 1990).

Rogers et al. (1988) surveyed 3000 randomly chosen physicians by mailed questionnaire to determine their knowledge, attitudes and behaviour to the US FDA reporting system. The response rate was 37%, of which 57% were aware of the FDA reporting system. It was indicated that unavailable report forms, events already

documented, lack of time and unawareness were the important reasons for the physicians not reporting the ADRs.

Moreover, the lack of co-operation and participation among health professionals including physicians, nurses and pharmacists was one of the main reasons for underreporting (Pschirer et al., 1990). A recent study by McGovern et al. (1998) demonstrated that information concerning ADRs resulting in changes in drug therapy was poorly communicated to primary healthcare professionals.

Pharmacists are one of the health professionals who play an important role in the reporting system in the USA. It is however possible that not all of them pay attention to ADR reporting. Therefore, pharmacists' knowledge and perceptions of their role in monitoring and reporting suspected drug reactions were determined. Of 235 Rhode Island pharmacists, those in retail settings were more likely to be aware of ADRs relating to therapeutic inequivalence and to ask patients about ADRs than were hospital pharmacists. Seventy five percent of all pharmacists were familiar with the FDA's SRS. However the practice setting, experience in the practice and the number of working hours influenced the reporting behaviour. Attitudes which deterred pharmacists from reporting ADRs were as follows: unsure which drug caused the reaction, do not have form, do not know how to report and reaction was expected (Generali et al., 1995). In Hong Kong, a much smaller proportion of pharmacists had actually reported ADRs, although they agreed that it is necessary to report them. Most pharmacists (87.4%) were not aware of any ADR reporting system. Unlike the previous study, there did not appear to be a relationship between ADR reporting behaviour and the length or place of practice, workload or patient contact time. The pharmacists perceived that severe or unusual ADRs and ADRs to newly marketed

drugs were significant enough to report which was similar to that found with Rhode Island pharmacists (Lee et al., 1994).

Lack of knowledge of an ADR reporting programme and poor attitudes towards the scheme have led to non-reporting. Therefore, improvement in knowledge and changing attitudes toward the SRS are important means by which to increase the reporting rate.

1.7 Role of pharmacists in ADR reporting systems

Pharmaceutical services in many countries are increasingly patient-oriented including involvement in ADR monitoring schemes. A survey undertaken in 1992 showed that 46% of pharmacies in National Health Service (NHS) hospitals in the UK operated the CSM ADR monitoring scheme and 13% also operated an additional ADR monitoring scheme (Cotter et al., 1994, 1996). In the USA, more than 95% of 248 federal hospitals participated in ADR programmes in 1993 and in approximately 70% of pharmacist interventions were documented in the medical records (Crawford and Santell, 1993). Thus, UK hospital pharmacists appear to provide less ADR monitoring services than those in the USA. However, USA pharmacists have been able to submit ADR reports to the FDA directly since 1962 which contrasts with UK pharmacists who have only been allowed to send yellow cards to the CSM since April 1997. Spencer (1985) suggested that the role of UK hospital pharmacists in ADR reporting systems had been neglected, although they were encouraged to participate in initiatives designed to increase awareness and improve the reporting rate.

Other countries such as Australia, Belgium, France, Germany, Ireland, New Zealand have also permitted pharmacists to directly contribute to the reporting system as a potential source of ADR reports, while pharmacists in Denmark, Finland, the Netherlands and Sweden, like UK pharmacists, have been excluded from supplying ADR reports to the national ADR reporting schemes (Roberts et al., 1994).

1.7.1 Role of UK pharmacists in ADR reporting

Previously, the yellow card system only accepted ADR reports from doctors, dentists, coroners and pharmaceutical companies (Committee on Safety of Medicines, 1997). Pharmacists in the UK were not given this opportunity despite ADRs presumably being drawn to their attention during the course of their work (Anonymous, 1993). As the yellow card scheme had been limited by gross underreporting, Veitch and Talbot (1985) and D' Arcy (1996) suggested that a possible way of increasing the reporting rate was to make reporting by doctors compulsory as in Sweden, however, this could be opposed by the doctors. Another feasible way was that pharmacists should be involved in the reporting process by encouraging doctors to report ADRs together with occasionally identifying reactions and taking responsibility for reporting themselves. Although a working party did not recommend direct reporting by pharmacists to the CSM, it acknowledged that pharmacists participating with doctors in ADR reporting should be introduced and further developed (Edwards et al., 1989). Randhawa et al. (1987) surveyed hospital doctors' opinions on whether pharmacists should be involved in the reporting scheme of the CSM. Of 60 doctors, 70% thought that pharmacists should report in conjunction with doctors while 20% thought pharmacists should report ADRs directly. In addition, several researchers demonstrated that both hospital and community pharmacists play a potential role in ADR reporting and monitoring (Roberts

et al., 1993; Whittlesea and Walker, 1996a,1996b; Bussey et al., 1985; Davis et al., 1999; Lee et al., 1997).

Eventually, all hospital pharmacists in the UK were allowed an official role in the national reporting scheme from 1 April 1997. However, community pharmacists in only four regional centres (Cardiff, Birmingham, Liverpool and Newcastle) are able to join in ADR demonstration schemes. These regional schemes will be evaluated before considering any further extension to pharmacist reporting (Anomymous, 1997; Anonymous, 1996).

1.7.1.1 The role of hospital pharmacists

A working party led by Grahame-Smith in 1986 provided advice to the CSM that the CSM should ask health authorities to encourage the participation of pharmacists in work on ADRs in hospital. However, they did not support direct reporting by pharmacists to the CSM. In contrast, the Nuffield report of 1986 supported the belief that there was a strong case for recognising the role of hospital pharmacists in ADR reporting (Nuffield Foundation, 1986).

There were several ADR monitoring schemes developed involving pharmacists to improve the ADR reporting rate. A pharmacy-based ADR reporting scheme (green card scheme) was established at the Royal Liverpool Hospital in 1984 which encouraged pharmacists, nurses and doctors to initiate reports. Subsequently, the reports were assessed weekly by a pharmacist and a clinical pharmacologist and forwarded to the CSM if the ADRs were considered to be serious or involved black triangle drugs. The rate of reporting increased nearly eight-fold after the beginning of the scheme (Winstanley et al., 1989). A similar scheme was developed for all medical

wards in the John Radcliffe hospital, Oxford. It provided a simple alert method using a locally designed yellow form at the end of the bed, with subsequent follow up, monitoring and validation of the reports by an ADR team consisting of a pharmacist and a clinical pharmacologist. The results also demonstrated a marked increase in the number of reported ADRs, with the incidence of 6% of patients possibly experiencing ADRs (Booth et al., 1988). In addition, Bussey et al. (1985) conducted a study to demonstrate that clinical pharmacists could improve the reporting of ADRs by working closely with clinicians. All suspected ADRs detected by the clinicians were passed to the clinical pharmacist for further investigation from medical notes, biomedical profiles, patient interviews and discussions with the clinicians. Over the 21 month period, a total of 79 suspected ADRs were observed and 44 reports were forwarded to the CSM, compared with two reports from the same setting in the 12 months prior to the study.

Some hospital pharmacists in the UK have been involved in setting up regional ADR reporting schemes which were operated in conjunction with the CSM, i.e. the West Midlands, Northern region and Wales. In 1990 a trial scheme to allow hospital pharmacists to sign the yellow cards and submit them to the CSM was announced (Anonymous, 1990). There was considerable evidence that the regional groups had increased the number of ADRs reported as described below.

In the Northern region, a pilot scheme was established to evaluate the contribution of hospital pharmacists in ADR reporting. In the early stage, three general hospitals were chosen to participate in the scheme and compared with four control hospitals. Reporting cards (green card) were placed on all wards, outpatient clinics and X-Ray departments. Health professionals were asked to record brief details of any suspected ADRs on green cards which were forwarded to the pharmacy department for further assessment and follow up by a pharmacist if necessary. Yellow cards were

completed by the clinician in collaboration with the pharmacist. It was revealed that the green card scheme tended to increase the number of yellow cards in one hospital and the quality of yellow cards originating from green cards was equivalent to those from control hospitals (Edwards et al., 1989). During 1992-1993, all hospital pharmacists within the region were asked to report any suspected ADRs by using the special report form which was similar to the yellow card. Subsequently, the ADR reports were sent to the Northern Regional Monitoring Centre for analysis. The results showed the reporting of ADRs in the region markedly increased by 45%, with a 54% increase in the reporting of serious reactions. Significantly more reports from hospital pharmacists concerned serious ADRs and new drugs than those from hospital medical staff. Pharmacists also generated 30% of all hospital reports in this region in 1992 and their report quality with regard to causality, appropriateness and completeness was comparable to those of doctors (Lee et al., 1997; Lee, 1993).

In Wales, the ADR scheme was established in 1983. All yellow cards issued were addressed to the medical assessor for the scheme and received in the department of pharmacology and therapeutics. The replacement card was subsequently forwarded to the reporting doctor, with a preliminary letter from the medical assessor. Also, an ADR bulletin was produced and distributed to all doctors every six months. It was concluded that not only was feedback to reporters on their contribution to this scheme recognised as useful, but also collaboration with doctors would prepare pharmacists for a future role in ADR reporting (Spencer, 1985).

In West Midlands region, drug information pharmacists played a key role in a devolved reporting system. Requests to drug information pharmacists about ADRs led to reporting to the CSM. Yellow cards were completed for approximately 10% of the 1824

ADR inquiries to the drug information centre during 1976-1981 at Good Hope Hospital in the West Midlands (Veitch and Talbot, 1985).

After the recent announcement from the CSM that hospital pharmacists are allowed to report the yellow card directly, Green et al. (1997) surveyed 200 hospitals in the UK by sending questionnaires to investigate the activity of hospital pharmacists involving ADR reporting. Of 172 respondents, local ADR reporting schemes were in operation in 26 (15%) pharmacy departments. Only 2.3% and 1.7% documented ADR details were in patients' notes and communicated to the patients' GPs, respectively. Time factors and lack of perceived need to operate a scheme were the main reasons for lack of a local ADR scheme. However, 80% of the settings without local schemes would consider implementing a scheme in the future. The authors suggested that local ADR schemes could encourage pharmacists to take a key role in this area. Recently, a survey to assess the role of hospital pharmacists in national ADR reporting after one year after of being allowed to report ADRs directly to the CSM showed that 64% of a total 185 pharmacy departments had submitted only five or fewer ADR reports to the CSM during this year, while 62% of the departments claimed to promote pharmacist reporting and education of pharmacists on ADR reporting was provided by 69% of pharmacies, the level of ADR reporting activity by pharmacy departments varied remarkably and in most cases was insufficiently developed (Ferguson and Dhillon, 1999).

A recent study undertaken by Davis et al. (1999) evaluated the suspected ADR reports submitted by hospital pharmacists to the CSM in the first year of their official role. During 1 April 1997 - 31 March 1998, 645 (3.1%) of a total 17,769 spontaneous reports were received directly from the UK hospital pharmacists. Hospital pharmacists sent a higher proportion of serious ADR reports but a lower proportion of reactions

related to black triangle drugs, compared with hospital doctors. This data suggested that hospital pharmacists made a valuable contribution to the yellow card scheme apart form the doctors, however, there was variability in levels of reporting from hospital pharmacists which needed continuing education to raise their role profile. A recent training programme for hospital pharmacists in ADR reporting was set up by Mersey regional monitoring centre in June 1998. It was shown that the number of ADRs reported in the month following the study day increased from an average of six to fourteen. Nevertheless, constant reminders were needed to alert the pharmacists to maintain the number of reports (Randall, 1999).

1.7.1.2 The role of community pharmacists

In 1992, the Department of Health and the Royal Pharmaceutical Society jointly published recommendations for an extended role for community pharmacists (Royal Pharmaceutical Society, 1992). Therefore, a study was performed to examine the views of community pharmacists and the Family Health Services Authorities (FHSAs) on those recommendations. Both community pharmacists (72%) and FHSAs (84%) agreed that pharmacists should report ADRs to the CSM directly and the Royal College of General Practitioners (RCGP) also accepted this suggestion (Sheppard et al., 1995). A similar study by Sutters and Nathan (1993a, 1993b) was undertaken to explore community pharmacists and general practitioners' attitudes towards extended pharmacy roles. The results showed 78% of community pharmacists and 85% of general practitioners supported community pharmacists' involvement in ADR monitoring, with no significant difference between professions. Both professions also agreed that the pharmaceutical industry should promote the role of community pharmacists in ADR monitoring. Bond et al. (1995) also found that 74% of a total of 266 general practitioners agreed on the extended role of community pharmacists in

formal ADR reporting system. A report of a meeting between the Royal Pharmaceutical Society and the RCGP also noted that the RCGP supported the reporting of ADRs by community pharmacists and their formal role in the ADR reporting system (Whittlesea and Walker, 1996a; Anonymous, 1992).

While the importance of over-the counter (OTC) drugs and self medication has increased markedly over the past decade in the UK, ADRs from these medicines are less likely to be recognised by doctors. It has been suggested that the potential role of community pharmacists should be developed by collecting and reporting ADRs to OTC drugs (Roberts et al., 1993).

A number of studies have emphasised the contribution made by community pharmacists in ADR reporting. Khan and Archer (1994) carried out a study over a six-week period to confirm the role of community pharmacists in ADR reporting. Ten randomly selected community pharmacies in Manchester participated in the study. There were 96 completed reports received, of which 70% were identified by the pharmacists, although the severity of most cases was mild. All the pharmacists believed they should submit ADR reports for OTC drugs and 90% wanted to submit reports on black triangle drugs to the CSM.

Whittlesea and Walker (1996a, 1996b) developed an ADR reporting scheme using the CSM criteria for community pharmacists holding patient medicine records (PMRs) in Wales and determined whether the pharmacists had appropriate knowledge and access to sufficient information to complete ADR reports. Of the 196 community pharmacies invited, 100 agreed to participate in the study. During the study period, 21 out of these participants sent 49 ADR reports, of which 12 reports related to black triangle drugs. A panel consisting of six pharmacists evaluated the ADR reports. One-

third of the reports were agreed by all the panel to be ADRs, while a further one-third of reports were considered to be ADRs by all except one member of panel. The number of complete fields for the reports ranged from 15 to 30 of the total 31 fields of information contained in the ADR report form. The researchers also evaluated the scheme by sending questionnaires to the participating pharmacists. The response rate was 70%. Of these, 87% and 75% indicated the preferred route was both to the CSM and the patient's GP for submitting the ADR reports of new drugs and prescription only medicines (POM), respectively. Fifty nine percent agreed with direct submission to the CSM solely for the OTC drugs. The results suggested that community pharmacists had the potential to report ADRs, with appropriate knowledge and were willing to commit the time to complete the reports (Whittlesea et al., 1993).

Wolfson et al. (1993) investigated the role of the UK community pharmacists in ADR reporting by conducting four linked studies. The first study determined the perception of the pharmacists about their role in ADR reporting by sending questionnaires to all 116 pharmacies in Bradford. The results showed 95% of the 61 respondents admitted that patients had presented to them with a symptom thought by the patient to be an ADR. Eighty two percent and 89% felt they should be involved in reporting ADRs to black triangle drugs and OTC drugs respectively, while 69% of them thought involvement in ADR reporting would require further education. The second study sought to determine whether any symptom described by patients presenting in pharmacies could be due to an ADR. The community pharmacists were asked to complete the form for all patients complaining of symptoms. A total of 342 completed forms were returned from 14 pharmacies. It was found that 22% of all patients presenting with symptoms were taking drugs before the onset of the symptom. Of 28 possible ADRs identified by the researchers, four were suitable to report to the CSM. The researchers estimated that approximately 20,000 yellow cards would result if this

pharmacy network applied across the UK. Study 3 aimed to investigate an ADR reporting scheme being established for pharmacists to report ADRs to a limited number of drugs and assess if their reports would be of value to the CSM. Of 75 pharmacists participating in the scheme, 26 forms were returned from 14 different pharmacies. The results suggested that ten reports would be of benefit to the CSM. Study 4 assessed the reasons for the low reporting rate in study 3 using a questionnaire survey. The results demonstrated that 63% of respondents did not complete the forms due to no ADRs being identified. After evaluating the four pilot areas, the authors recommended that reporting of ADRs by community pharmacists was feasible and of benefit to the CSM, however, further education should be arranged. Pharmacists should report ADRs directly to the CSM as well as to the GP. Also, patient medical records were suggested as a useful tool in identification and reporting of ADRs.

A more recent study by Green et al. (1999) investigated pharmacists' attitudes and knowledge of ADR reporting and the Yellow Card scheme in 40 randomly selected community pharmacies within one demonstration scheme area. It was found that almost all of the pharmacists (93%) were aware that they were able to report ADRs but only one had done so. The main reasons for not submitting reports were lack of time and the reactions identified were well-recognised. Few pharmacists knew the reporting criteria for ' black triangle' drugs. Although reporting on OTC drugs is a potential role of community pharmacists, 70% of them agreed that they would be unlikely to report an ADR related to the OTC drugs. However, most agreed that ADR reporting is important area in which pharmacists should be involved.

1.7.2 Role of pharmacists outside the UK

Pharmacists in several countries are able to participate in national ADR reporting systems. Hospital-based pharmacists more often get involved in ADR schemes than those in community. In Canada, one in every six hospitalised patients has experienced an ADR (Taras-Zosowski and Einarson, 1989), therefore, pharmacists' contribution to the ADR programme helps to reduce the financial burden of ADRs. In the Netherlands, a regional pharmacy-based ADR surveillance scheme showed that the contributions of doctors and pharmacists prevented iatrogenic damage. Community pharmacists also played a key role in drug monitoring (Roberts et al., 1994). Additionally, in 1984 a regional spontaneous reporting system was set up to collect and evaluate suspected ADRs. ADRs reported by doctors were collected and passed to a pharmacist for additional information as well as an assessment of the causal relationship between the reaction and the suspected drug. The complete report was then sent to a centre known as the Netherlands Pharmacovigilance Foundation (LAREB). A total of 22,000 ADR reports were received by LAREB at the end of 1995 and about 15% of these were previously unknown ADRs (de Koning et al., 1997).

In the USA, in 1985 90% of ADR reports were submitted by drug companies, while health professionals reported the remaining 10%, of which one-third was from pharmacists. Pharmacists had been significantly involved in the setting up of ADR reporting programmes within institutional settings due to the requirements mandated by the US Joint Commission of the Accreditation of Healthcare Organizations (JCAHO). These ADR schemes varied from hospital to hospital but satisfied JCAHO requirements (Fincham, 1989). According to American Society of Health-system Pharmacists (ASHP) guidelines, a comprehensive ADR monitoring and reporting programme should be an integral part of an organisation's drug use system and

pharmacists should exert leadership in the development, maintenance, and ongoing evaluation of ADR programmes (American Society of Health-system Pharmacists, 1995). Tyler and Nickman (1992) surveyed 444 randomly selected hospitals by sending questionnaires to directors of pharmacy and revealed 90% of 176 respondents met all of the JCAHO standard and 28% complied with all of the ASHP guidelines. Ninety seven percent of the hospitals had policies for ADR reporting. A study of Herrera et al. (1992) found 96% of 61 responding hospitals collected information on ADRs, with 22% indicating their surveillance system as active. The professionals most often cited as responsible for the systems included pharmacists, assurance personnel and nurses.

Close interaction between doctors and pharmacists was listed as one of the key features of a hospital ADR surveillance system described by Gilroy et al. (1990) which could contribute to a substantial increase in reporting. There are many other examples of schemes involving pharmacists which have also resulted in higher frequencies of ADR reports (Mahoney et al., 1991; Shuban, 1991; Saltiel et al., 1995; Wu et al., 1992; Zoka et al., 1994; Upchurch et al., 1991; Wessenberg et al., 1993).

Since ADRs are one of the commonest drug-related problems resulting in clinical intervention (Alderman, 1997) and as already noted, many ADRs are preventable (see Section 1.1.3) the use of systematic surveillance schemes has provided an opportunity for pharmacists to reduce morbidity associated with ADRs (Evans et al., 1994). The involvement of pharmacists in both formal and informal ADR reporting can thus contribute significantly to improvements in patient care.

1.8 Patient-self reporting of ADRs

None of the formal PMS systems fare very well in detecting new ADRs because of lack of appropriate control groups (Solovitz et al., 1987). They also have problems in validating the causality of reported symptoms and require a great deal of additional information to rule out non-drug causes. Another method which could be useful is patient-self reporting of symptoms related to drugs. ADR reports direct from patients are included in the national ADR registers in the USA and Germany (Roberts et al., 1993). Most suspected ADRs in outpatient populations were initiated by patients' reports to their doctors, but there is little published literature regarding the development of formal patient-initiated surveillance approaches (Fisher and Bryant, 1992).

1.8.1 Community pharmacist involvement in patient-self reporting of ADRs

There are a limited number of studies in the area of patient self-reporting of ADRs with which pharmacists have been involved. Those studies are described below.

Campbell and Howie (1988) initiated a method for increasing the reporting rate of ADRs by using patient-self reporting of ADRs. A total of 896 patients prescribed one of 77 black triangle drugs were given a leaflet by the community pharmacists and encouraged to report any adverse reaction to their doctors. The doctors were also asked to review the case notes to assess whether the adverse reaction reported could be attributed to the suspected drug. The results showed that reports of ADRs increased from ten per 1000 in the two-month control period to 23 per 1000 in the two-

month intervention period. Surprisingly however, only one yellow card was sent to the CSM during the study period.

Fisher et al. (1987a, 1995) and Fisher and Bryant (1992) conducted a patient-initiated, pharmacy-based PMS study at the University of Texas Medical Branch. Initially 2705 randomly selected outpatients prescribed antibiotics and tricyclic antidepressants as an experimental group had a printed notice attached to their medication bags. The patients were requested to report any new or unusual symptoms during the next two weeks by calling a toll-free telephone number to a trained ADR interviewer. Another sample of 1109 patients acted as a control group and did not receive the information but were interviewed by telephone two weeks later. The results demonstrated both experimental and control groups reported predictably high relative frequencies for the most commonly known ADRs to these drugs. These researchers concluded that patient-self monitoring could be a promising complement to existing doctor-based reporting systems as well as a possible early alert mechanism for detecting ADRs to new drugs. The researchers also performed a pilot study offering different levels of compensation for study participants. It was revealed that the percentage of acceptance for the full sample of volunteers was related to the amount of compensation given with $25 resulting in a 59% increase and $10 resulting in a 34% increase in acceptance (Bryant et al., 1990). Fisher et al. (1995) also used the same method via a free-phone interview to compare ADRs reported by a large sample of outpatients prescribed fluoxetine and sertraline. Data were collected on 1577 fluoxetine-treated and 1209 sertraline-treated patients who filled their prescriptions at 596 different pharmacies nationwide. The data indicated 34% of patients on sertraline called at least once to report one or more ADRs compared with 20% of patients on fluoxetine. Most of the reported symptoms were expected ADRs. A further study by the same authors planned to involve 700 Texas pharmacies with a goal to monitor at

least 10,000 patients treated with a particular target drug in order to detect relatively rare ADRs over a five-year period. Nevertheless, there has been a lack of support for this method from both the US FDA and the pharmaceutical industry (Fisher et al., 1987b; Fisher, 1995). A similar study (Fisher et al., 1993) compared incidence estimates and relative risk for a number of ADRs experienced by 815 trazodone-treated and 2487 fluoxetine-treated patients.

Mitchell et al. (1988,1989,1994) suggested event reporting was reliable and had greater sensitivity than reaction reporting for detecting true ADRs. A subsequent study was carried out to investigate the potential of patient reports of ADRs in a region of Australia. Eighty community pharmacists were asked to distribute event report forms consisting of 35 questions to consecutive patients presenting prescriptions for either diclofenac or piroxicam. Patients were asked to complete the form one month after it was received. Drug-free subjects and spontaneous reports submitted by health professionals to the national reporting system were also recruited to compare with the study group. Of the 1559 report forms distributed, 39% were returned. Patient-self reporting identified established ADRs compared with the drug-free subjects, while reports from health professionals tended to report more severe but rarer reactions than patient-self reports. The authors suggested that the system based on patient-self reporting could increase sources of information on ADRs that were important to patients and might generate early warning of symptomatic reactions to new drugs.

In addition, a prospective observational study based on telephone interviews with 1475 patients presenting prescriptions for NSAIDs at five community pharmacies was conducted in a region of Canada. Of the patients approached, 51% participated and 83% of these provided completed interviews. It was found that 19% of recruited patients reported a new health problem or unusual symptoms at the initial interview. Of

the total 183 reported health problems, 86% affected the GI system (Willison et al., 1995).

Egberts et al. (1996) compared the time to reporting of ADRs by patients and by health professionals for a newly introduced antidepressant, paroxetine. Data from patients who consulted a pharmacist via a free telephone medicine information service during 1992-1994 were searched for those indicating an ADR related to paroxetine. The results showed the mean lag time for all suspected reactions to paroxetine by patient self-reporting was 229 days less than for reports submitted by health professionals to the Pharmacovigilance Foundation in the Netherlands. The proportion of new ADRs was comparable for both systems. These workers suggested that, although the patient reporting might generate false alarms, it may play an additional role in pharmacovigilance as it enabled earlier detection of ADRs. A recent study by van den Bemt et al. (1999) evaluated the relative value of ADRs reported by doctors, nurses and by patients on four wards of two hospitals in the Netherlands over a two-month period. The ADRs were collected by spontaneous reporting from doctors and nurses and by patient reporting via an interview with a hospital pharmacist. The pharmacist asked the patients whether they experienced any ADRs on the previous day. If so, the patients were asked further information about the time relationship. Of a total 620 patients, ADRs were reported in 29%. It was revealed that doctors reported a statistically significant higher number of serious and unknown ADRs than those reported by patients and nurses. Interestingly, adverse reactions to newly marketed drugs were only reported by patients which accounted for 8% of all daily ward visit reports. Therefore, pharmacist-assisted patient-self reporting might be useful for detecting adverse reactions caused by newly marketed drugs.

It has also been suggested that patients' drug related concerns can be identified using a brief medication questionnaire with a mixture of closed and open-ended questions and indirect and direct questions which could easily be incorporated by pharmacists into their normal routine (Svarstad, 1998). A study using the questionnaire to screen drug related concerns in asthma patients in pharmacy practice found 50% of the patients had experienced bothersome effects of drugs (Anonymous, 1998).

1.8.2 Patient-reported adverse effects to specific drugs

Several studies have been described in which patients have been asked to record the presence and/or severity of side effects resulting from a specific drug group. In general, these consist of lists of potential adverse effects and patients consistently identify well-recognised symptoms as well as other, perhaps unanticipated, effects. Alopecia, fatigue, and taste change were among the most common side effects identified by patients receiving chemotherapy with the well known CHOP regime (Sitzia et al., 1997), while fatigue was both the most common and the most troublesome side effect of carboplatin (Buckingham et al., 1997). Patients receiving antiepileptic drugs identified mood changes and irritability, general cognitive difficulties and fatigue, although the latter was the only symptom which was more common in drug-treated patients than in controls (Brown and Tomlinson, 1982). Scottish patients treated with lithium for affective disorders selected symptoms known to be adverse effects of the drug significantly more frequently than 'dummy' symptoms (Nicol, 1998), while Hong Kong Chinese patients also selected symptoms known to be adverse effects to lithium from checklists (Lee, 1993). Rickels and Downing (1970), using checklists in patients treated with tranquilizers or antidepressants and controls, showed that four of the six most commonly cited symptoms corresponding to known

adverse effects were significantly more frequent in drug-treated respondents than in controls.

The use of checklists which include a range of selected potential adverse effects, mostly known already to be associated with the drugs under study, are clearly not appropriate for the detection of previously unknown adverse effects or for general use. Such checklists therefore have limited application, although they do show that patients are capable of identifying adverse effects.

1.8.3 Attribution of events to drug therapy by patients

There are further studies which suggest that patients are capable of correctly attributing adverse events to drug therapy. A study by Sorovitz et al. (1987) involved the development of a complete listing of possible ADRs selected from Long (1977) and the US Pharmacopoeia 1983. Using interviews, these workers showed that patients correctly attributed possible ADRs to the target drug (antidepressant or antibiotic) more frequently (69%) than other symptoms (43%). Nevertheless, Fisher and Bryant (1990) suggested that attribution accuracy depended both on the surveillance method and on how reports were obtained. Discrimination was better when patients reported adverse events spontaneously than when through systematic enquiry by an interviewer. The use of a systematic enquiry following a patient-initiated telephone call by patients who have experienced possible side effects following use of a drug has been shown to identify different effects with different antidepressants (Fisher et al., 1993, 1994). These authors suggested that by asking patients to attribute symptoms to a particular drug they are less likely to accrue false positives than using methods which document all health changes after initiation of medication, such as PEM.

Specific questioning using checklists was found by Rickels and Downing (1970) not to increase the number of drug-related symptoms identified through suggestion, since symptoms not known to be related to drugs did not differ in frequency between drug-treated patients and untreated controls.

It is therefore possible that patient self-reporting could identify previously unknown adverse effects, provided sufficiently large numbers of patients are studied. These methods could also be used to identify problems more rapidly than health professional-initiated reporting systems (Egberts et al., 1996). In addition these methods could be used to obtain more realistic estimates of the incidence of minor adverse effects, since these are more likely to be reported by patients (Mitchell et al., 1994)

1.8.4 Factors affecting patient self-reporting of ADRs

Older patients are more likely to experience ADRs than younger patients because the ageing process is associated with both physiological and pathological decline in most body systems (Beard, 1992). However the elderly may under-report symptoms, possibly because of the perception that many symptoms may be regarded as part of the natural process of ageing, rather than being drug-related (Morgan et al., 1997). Indeed, increasing age appeared in one study of those over 65 to be associated with a decreased tendency to report symptoms using an open questionnaire (Chrischilles et al., 1992). This could include a reduced ability to detect and report ADRs in the very elderly. Conversely, Bryant et al. (1991, 1992) found that those aged 50 or over were possibly better at discriminating probable ADRs from other types of adverse events than were younger patients.

Hospitalised patients were reported to be more likely to report ADRs than those attending outpatient clinics or in the community in one study (Mannesse et al., 1997). These patients, however, were less likely to recognise severe reactions than mild ones and the frequency of reactions reported was related to the number of drugs being taken, rather than to the number of disease states present.

1.8.5 Comparison of methods used in patient self-reporting

The three methods commonly used to detect ADRs by patient self-reporting are open questions, systematic assessment using a symptom checklist and spontaneous reporting (Corso et al., 1992). A systematic enquiry combined with spontaneous reporting appears to more than double detection rates compared to spontaneous reporting alone (Fisher et al., 1987c). However the latter appears to be most reliable for unexpected ADRs, although the actual incidences may be underestimated (Barber and Santanello, 1995). While an open-ended questionnaire has the advantage of not suggesting adverse effects to patients, the symptom checklist can encourage reporting of symptoms which patients may otherwise fail to report. In a comparison of these two methods in 515 patients treated with bacampicillin, a greater frequency of ADRs was reported using the checklist, although the events reported in response to the open questions were in general more serious (Wallin and Sjovall, 1981). As a result these authors suggested that a combination of the two methods was optimal in detecting ADRs. Downing et al. (1970) also found a higher frequency of reported adverse effects using a structured checklist than an open question. As mentioned in section 1.8.3, the checklist did not suggest adverse effects to the untreated control group included in this work. Spontaneous reporting was found by Rosenthal et al. (1996) to result in a lower overall prevalence of adverse events than when identified by a standard questionnaire.

These studies confirm other work showing that open questioning of healthy individuals and those on medication results in fewer symptoms being reported than the use of checklists (Ciccolunghi and Chaudri, 1975). These workers however also found that more severe symptoms were reported using open questions, which is in line with the more serious nature of spontaneously reported events found by Wallin and Sjovall (1981). This was also confirmed by the findings of Barber and Santanello (1995) in that more bothersome effects were reported spontaneously, although most patients who completed a checklist in their study had experienced some adverse effects.

Open questions and checklists were also compared with doctors' reports by Borghi et al. (1984). These workers found that open questions provided more information about the symptoms of disease than the unwanted effects of drugs. The checklist seemed to suggest mild signs and symptoms to the patients. They concluded that conventional reporting by doctors appeared to provide more reliable information about adverse effects. The view that questionnaire-obtained reports of side effects are relatively poor was also held by Curb et al. (1985), since they found that many fewer patients had their drug discontinued because of the reported side effects than for other reasons.

While acknowledging that patients may not be qualified to decide on the attribution of symptoms, may only spontaneously report those adverse effects which are most bothersome and may be prompted by checklists to report symptoms with high frequency, the fact remains that patient perceived adverse effects are a common cause of failure to comply with medication regimens (Stockwell and Schulz, 1992). It is therefore important to obtain information about patients' perceptions of adverse effects.

Corso et al. (1992) developed a questionnaire containing a comprehensive list of symptoms in lay terminology categorised by body system in order to overcome the overestimation of ADR incidence which is common with checklists. This was used as part of a computer-assisted interview to obtain information from patients regarding their medication regimens and the presence of complaints. The list of symptoms was extracted from the United Sates Pharmacopoeia Dispensing Information (USPDI) computerised database. This comprehensive list was deliberately designed to eliminate the bias and false positive responses, since patients were asked about all potential ADRs, not just those known to be associated with the specific drugs. It was suggested that this list may also improve patients' ability to identify and report symptoms experienced.

1.9 Reasons for undertaking this study

Pharmacists in many countries are changing their roles, particularly in primary care. Many projects have identified areas in which the involvement of pharmacists can improve patient care and the recent involvement of pharmacists in ADR reporting has similarly shown they can enhance the existing system. Many patients suffer from ADRs (see Section 1.1.2), many are caused by physician prescribing decisions (Bates et al., 1993), yet many are preventable (see Section 1.1.3). As pharmacists increase their contact with patients the opportunities for prevention of ADRs also increases.

The majority of work on ADR reporting has not however involved patients directly, yet the main methods of detecting ADRs currently in use in the UK rely on the patient spontaneously reporting symptoms to prescribers. The actual incidence of ADRs could be considerably higher (Gill et al., 1995) and could contribute to patients not taking

medicines. Patients' involvement in treatment decisions is increasing (The Royal Pharmaceutical Society of Great Britain, 1997), yet their experiences of using drugs are not routinely sought. A questionnaire which enables patients to report their perceptions of adverse drug effects could thus be of value in different situations, for example to assist in identifying ADRs to new drugs or to identify problems during routine monitoring of therapy.

Therefore, the purpose of this study was to develop and validate such a questionnaire and to evaluate its use in identifying ADRs to new, black triangle drugs.

1.10 Objectives of the present study

The present study was divided into two phases.

Phase I: Pilot study

1. To develop and validate a questionnaire for patients to complete to enable detection of potential ADRs.
2. To determine the frequency of potential ADRs reported by patients using this questionnaire to five established central nervous system (CNS) drugs.
3. To compare patients' reports of potential ADRs to those reported in their GP medical records.
4. To evaluate the potential accuracy of patients' attribution of symptoms to the five drugs by classification of the symptoms using causality assessment.

Phase II: Main study

1. To identify a sufficiently large population of patients prescribed one of nine new drugs to enable the generation of meaningful data on their perceptions of potential ADRs to these drugs.
2. To identify the frequency and rate of self-reported ADRs to these drugs.
3. To compare patients' reports to the documentation of these reactions by GPs for a sample of the reports.
4. To compare patients' and GPs' reports to those received by the CSM for the same period.
5. To evaluate the potential accuracy of patients' attribution of symptoms to the new drugs by classification of the symptoms using causality assessment.
6. To obtain an external comparison of whether the individual symptom classifications are appropriate or agreed.
7. To compare the rates of ADRs reported by patients to the nine new drugs with nation-wide data from the CSM, data from PEM, published data and the five established drugs from the pilot study.

Chapter 2

Methods

2.1 General

Prior to commencing research, permission to undertake the study was obtained from the Joint Ethical Committee of Grampian Health Board and the University of Aberdeen (Appendix A) and permission to access prescriptions was obtained from the Pharmacy Practice Division (PPD). The MCA was also approached to ensure that data from yellow card reports was available.

2.2 Questionnaire design

The questionnaire for detecting potential adverse drug reactions designed by Corso et al. (1992) and the standardised interview used to identify, describe and quantify symptoms by Fisher et al. (1987a) were used as a basis for the questionnaire. Two different types of questionnaire were designed, one involving closed questions and one open questions (Appendix B). The closed questions comprised a list of potential symptoms in all body systems. This questionnaire also provided an opportunity to add other symptoms or complaints for each body system using an open question. The open questionnaire provided spaces for patients to fill in the symptoms from which they considered to be caused by the study drug in each body system. Both questionnaires also requested information about the dose and frequency of the study drug, its indication and the start and stop dates of any other concomitant drugs. Both questionnaires were designed to ensure that all potential symptoms which

respondents considered could be due to the study drug could be included, by covering all body systems.

Lists of patients prescribed one of four CNS drugs were obtained from the repeat prescriptions of one general medical practice in Aberdeen. These drugs were two established drugs namely trazodone, amitriptyline and two new drugs namely tramadol and moclobemide. A small sample of 14 patients whom the GPs thought would willingly help with the study were sent both questionnaires by mail. Subsequently all those who agreed were visited at home in order to ask their views on the two types of questionnaire and to determine their ability to complete the questionnaires and whether they were worried by any aspect of them.

The patients views were summarised, the results from the two questionnaires compared and this data reviewed by the study team. The list of symptoms was found to be easier to complete than the open-ended questions by all patients and neither caused concern in any patient. Therefore this approach was used in further development. Some questions were also modified following the interviews (see Section 3.3.1).

The questionnaire developed from the pre-pilot study was divided into three parts.

- Part I concerned basic demographic information about patients and their medicines including the patient's sex, age, dose and frequency of study drug taken, start date and indication for the study drug. It asked patients to list other concomitant drugs along with whether they were started before or after the study drug and whether they had been stopped or not, other medical conditions, and requested information on any hospital admissions since starting the study drug as well as reasons for admission.

- Part 2 asked patients about their experiences of possible side effects. The symptoms listed were categorised into 19 body systems or anatomic regions. There was also a sub-question included in each body system which asked whether patients had experienced any other symptoms not listed and if so, to specify the symptoms. In addition, part 2 contained questions asking patients to identify the most bothersome symptoms, rate the severity of the most bothersome symptoms and state whether they had informed their doctors about all, some or none of them.
- Part 3 was only for completion by patients who had stopped taking the study drug. It requested the stop date of the study drug, reasons for stopping the drug, which, if any, symptoms had disappeared and whether any other symptoms had started after discontinuing the drug.

The final questionnaire included a covering letter which confirmed to patients that all information collected would be treated in the strictest confidence and there would be no effect on their future medical care if they declined to take part. Reassurance was also given that their medicine did not cause all the effects or symptoms listed in the questionnaire. Care was taken in the design of the questionnaire to take account of previous research on colour and layout (Oppenheim, 1992) and to emphasise on each page that patients should identify only symptoms which they thought could be side effects of the study drug (see Appendix C).

2.3 Definition of ADR

The definition of ADR used in the present study was derived from that of the World Health Organisation (WHO). Thus any patient who identified a symptom which they perceived to be the result of an ADR defined as experiencing 'a noxious, unintended

effect of a drug that occurs at a dose normally used in humans for therapy, prophylaxis, or diagnosis'. This included unwanted pharmacological actions of a drug, excessive effects of the intended pharmacological action of a drug and idiosyncratic or allergic reactions. Intentional and accidental overdose, drug abuse and drug interaction were excluded from this definition.

2.4 Criteria for assessment causal relationship

The information available for assessment of causal relationship was that from self-reports completed by patients and patient medical records in some cases. Consequently, none of the classification systems described in Chapter 1 could be used. New criteria for classifying each symptom reported by patients were therefore devised. The logical categories developed accounted for the probability of a causal relationship between symptoms reported and study drugs, concomitant drugs or disease states. These criteria allowed symptoms to be classified into eight categories as follows:

1. Symptom caused by the study drug
    - known or previously reported reaction to study drug **and**
    - could not reasonably be explained by the effects of concomitant drug(s) **and**
    - could not reasonably be explained by the known characteristics of the patient's clinical condition
2. Symptom caused by the study drug and concomitant drug(s)
    - known or previously reported reaction to study drug **and**
    - could reasonably be explained by the effects of concomitant drug(s) **and**
    - could not reasonably be explained by the known characteristics of the patient's clinical condition

3. Symptom caused by the study drug and disease(s)
    - known or previously reported reaction to study drug **and**
    - could not reasonably be explained by the effects of concomitant drug(s) **and**
    - could reasonably be explained by the known characteristics of the patient's clinical condition
4. Symptom caused by the study drug, concomitant drug(s) and disease(s)
    - known or previously reported reaction to study drug **and**
    - could reasonably be explained by the effects of concomitant drug(s) **and**
    - could reasonably be explained by the known characteristics of the patient's clinical condition
5. Symptom caused by only concomitant drug(s)
    - not known or not previously reported reaction to study drug **and**
    - could reasonably be explained by the effects of concomitant drug(s) **and**
    - could not reasonably be explained by the known characteristics of the patient's clinical condition
6. Symptom caused by only disease(s)
    - not known or not previously reported reaction to study drug **and**
    - could not reasonably be explained by the effects of concomitant drug(s) **and**
    - could reasonably be explained by the known characteristics of the patient's clinical condition
7. Symptom caused by concomitant drug(s) and disease(s)
    - not known or previously reported reaction to study drug **and**
    - could reasonably be explained by the effects of concomitant drug(s) **and**
    - could reasonably be explained by the known characteristics of the patient's clinical condition
8. Unclassified
    - not known or not previously reported reaction to study drug **and**

- could not reasonably be explained by the effects of concomitant drug(s) **and**
- could not reasonably be explained by the known characteristics of the patient's clinical condition

These eight categories were then grouped into four categories according to the probability of the causal relationship. The presence of an ADR was classified as probable, possible, unlikely, or unattributable depending on which criteria were satisfied.

Criteria 1 = Probable: symptom probably caused by the study drug

Criteria 2-4 = Possible: symptom possibly caused by the study drug

Criteria 5-7 = Unlikely: symptom unlikely to be caused by the study drug

Criteria 8 = Unattributable: potential previously unreported symptom to study drug and unattributable to other drugs or disease states

Furthermore, the criteria on which the four categories were based were adapted for ease of use in classifying the reported symptoms. These criteria were used to provide an external comparison of whether the individual symptom classifications were appropriate or agreed. The modified criteria used for expert validation are listed below:

1. Symptom caused by the study drug
   - known or previously reported reaction to study drug **and**
   - could not reasonably be explained by the effects of concomitant drug(s) **and**
   - could not reasonably be explained by the known characteristics of the patient's clinical condition
2. Symptom caused by the study drug and concomitant drug(s), **and/ or** by disease(s)
   - known or previously reported reaction to study drug **and**

- could reasonably be explained by the effects of concomitant drug(s) **and/ or** by the known characteristics of the patient's clinical condition

3. Symptom caused by only concomitant drug(s) **and/ or** disease(s)
   - not known or not previously reported reaction to study drug **and**
   - could reasonably be explained by the effects of concomitant drug(s) **and/ or** by the known characteristics of the patient's clinical condition
4. Unclassified
   - not known or not previously reported reaction to study drug **and**
   - could not reasonably be explained by the effects of concomitant drug(s) **and**
   - could not reasonably be explained by the known characteristics of the patient's clinical condition

These classifications were graded into the same four probabilities of causal relationship as the previous eight criteria.

Criteria 1 = Probable: the symptom probably caused by the study drug

Criteria 2 = Possible: the symptom possibly caused by the study drug

Criteria 3 = Unlikely: the symptom unlikely to be caused by the study drug

Criteria 4 = Unattributable: potential previously unreported symptom to study drug and unattributable to other drugs or disease states

2.5 Pilot study

The purpose of the pilot study was to validate the questionnaire by using well-established drugs with known side effect profiles and using information from medical records to assess the completeness and accuracy of patient responses. It also enabled the researcher to gain practice in identifying adverse reactions to known drugs and provided further experience with the questionnaire prior to studying new drugs with less well-established side effect profiles. It was estimated that 50 patients taking each drug would provide sufficient data to validate the questionnaire.

Three medical practices with which links had already been established were asked to allow patients from their lists to be included in the pilot study.

2.5.1 Patient selection

2.5.1.1 Inclusion criteria

1. Patients prescribed one of five established CNS drugs; trazodone (Molipaxin®), doxepin (Sinequan®), sodium valproate (Epilim®, Convulex®), carbamazepine (Tegretol®) or co-proxamol via the repeat prescribing system.
2. Age 16 and over.

2.5.1.2 Exclusion criteria

1. Patients aged less than 16.
2. Patients resident in nursing homes.

2.5.2 Questionnaire distribution

Postal, pre-paid enveloped questionnaires (Appendix C) were sent to all patients prescribed carbamazepine, sodium valproate and trazodone from the three participating general practices. The questionnaires were sent to all patients prescribed doxepin and co-proxamol from two general practices and a random selection from another practice in order to achieve the aim of approximately 50 questionnaires returned from patients prescribed each study drug. If responses were not received within one month, reminder letters (Appendix D) and further questionnaires were sent to non-respondents. No follow up beyond the second mailing was attempted.

2.5.3 Data validation and evaluation

The responses to all questionnaires returned in which patients who reported a symptom were compared to information obtained by examination of the patients' medical notes. The aims of this process were to validate and clarify the information which patients had provided in the questionnaires and to obtain additional information such as strength of study drugs, other drugs taken or other disease states, where this had not been completed in the questionnaire. A data collecting form was designed for recording relevant information from the medical notes (see Appendix E). The details of information retrieved from the medical notes were as follows:

- Study drug: drug strength and dosage regimen, indication for use, start date, stop date (if patients had stopped taking the drug), whether symptoms reported by patients were recorded in medical notes and whether they were recorded as symptoms or side effects, date of recording in the medical notes for individual symptoms

- Concomitant drugs: name of other drugs taken concomitantly, start date, stop date
- Disease states with the year of diagnosis, whether the disease states were active problems (if available)
- Other relevant data (if available) such as laboratory results which may be related to the symptoms reported, drug allergy, alcohol intake, cigarette smoking, patient's weight.

After collecting data from medical notes, each symptom reported in Part 2 of the questionnaire was evaluated and categorised into one of the eight criteria for causality described in Section 2.4 using data from Part 1 and further information obtained from the medical notes. Information sources of known ADRs for the study drugs and the concomitant drugs were British National Formulary (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 1998), ABPI Compendium of Data Sheets and Summaries of Product Characteristics (The Association of the British Pharmaceutical Industry, 1998), Drugdex Drug Evaluation Monograph (1998), Meyler's Side Effects of Drugs: an encyclopedia of adverse reactions and interactions (Dukes et al., 1996) and common ADRs reported in the CSM data. Reference sources of symptoms related to the disease states included Davidson's Principles and Practice of Medicine (Edwards et al., 1995), Textbook of Therapeutics: Drug and Disease Management (Herfindal and Gourley, 1996), Manual of Medical Therapeutics (Woodley and Whelen, 1992) and Harrison's Principles of Internal Medicine: Companion Handbook (Isselbacher et al, 1994).

2.6 Main study

The main study involved distribution of the questionnaire to patients throughout Grampian who had been prescribed one of nine 'black triangle' drugs, validation of a sample of these by review of medical notes, evaluation and comparison to other reports of ADRs from CSM, PEM and other sources and external validation of the classification.

The questionnaire was modified in minor details after being used in the pilot study to ensure its appropriateness (Appendix F). Presently, doctors and hospital pharmacists are asked to report all suspected reactions, i.e. any adverse or any unexpected event, however minor, which could conceivably be attributed to newly marketed drugs indicated by the inverse black triangle symbol. Despite uncertainty about the causal relationship, reports to the CSM should be made regardless of whether the reaction is well recognised, and even if other drugs have been given concurrently. Therefore, symptoms reported by patients which were considered to be probable, possible or previously unknown reactions could be regarded as complementary to the existing reporting system. Estimation of the number of cases in which such symptoms were identified could thus be used to evaluate the usefulness of the questionnaire for identifying ADRs to new drugs.

2.6.1 Patient selection

All general practices in Grampian were approached by sending a letter to the senior partner in each practice (Appendix G) asking their permission for questionnaires to be sent to their patients. Of the total of 97 medical practices, 79 were willing to participate

in the study. The participating general practices were sent a reminder letter (Appendix H) and a sample of the final questionnaire before the questionnaires were sent to their patients.

2.6.1.1 Inclusion criteria

1. Patients taking one of nine black triangle drugs which were four antidepressants [venlafaxine (Efexor®), nefazodone (Dutonin®), citalopram (Cipramil®) moclobemide (Manerix®)], three anticonvulsants [gabapentin (Neurotin®), lamotrigine (Lamictal®), topiramate (Topamax®)] and two analgesics [tramadol (Zydol®), fentanyl patch (Durogesic®)]. All these drugs were given a black triangle symbol by the CSM issued in the British National Formulary (BNF), Data Sheet Compendium and Monthly index of Medical Specialists (MIMS) at the time of the study.
2. Each prescription dispensed for the study drugs which had been issued by the 79 participating practices in Grampian over the study period (January to March 1997) was identified by the Pharmacy Practice Division (PPD) in Edinburgh, using a search for the drug names listed above. The identification provided was in the form of a unique number with which all prescriptions are issued during the computerised pricing process. Patients' names and addresses were not captured as part of this process, therefore the actual prescription forms had to be accessed to obtain this information. The numbers provided were used to search manually through the prescription forms (GP10s) held at the PPD office in Aberdeen and the patients' names and addresses were copied from the prescription.
3. Patients who were prescribed a study drug at least once during the study period. Patients who were prescribed more than one individual drug studied were sent all relevant questionnaires.

4. Age 16 and over.

2.6.1.2 Exclusion criteria

1. Patients who had been prescribed the same study drug(s) more than once during January-March 1997 were excluded from a second mailing by using a computer programme set up for this purpose.
2. Patients aged under 16.
3. Those patients who lived in nursing homes.

2.6.2 Questionnaire distribution

Postal questionnaires with pre-paid envelopes were sent to the patients to determine their perceived ADRs to the new drugs. The questionnaires sent to patients receiving the antidepressants venlafaxine, nefazodone and citalopram, the analgesic drugs tramadol and fentanyl patch and the anticonvulsants gabapentin, lamotrigine and topiramate. There were no reminders sent to the non-respondents as it was felt that this may upset patients who had serious illness and were not willing to participate in the study.

2.6.3 Data validation and evaluation

A sample of the questionnaires received were validated using a similar method to that used in the pilot study. Since the largest number of questionnaires concerned tramadol and venlafaxine, these were selected for the validation process. Permission was sought from eleven practices to access the medical records of their patients who

had responded to the questionnaire. The practices were selected on the basis that a) a substantial number of questionnaires relating to these drugs had been returned and b) there was already a working relationship with a pharmacist to enable access to be obtained easily. The data obtained from the medical records was as described in Section 2.5.3. A total of 53 questionnaires concerning tramadol and 50 venlafaxine questionnaires were validated in this way. All symptoms reported by all respondents were evaluated and categorised for causality using the criteria described in Section 2.4.

The 103 cases for which additional data had been obtained from medical notes were further evaluated by asking an expert on adverse drug reactions, who was formerly a senior pharmacist at the CSM Regional Reporting Unit, Newcastle-upon-Tyne, to independently categorise the symptoms reported by these patients for causality, using the criteria described in Section 2.4. The classifications made were compared to those made by the researcher for the same cases.

2.6.4 Comparison to yellow card reports

Information was obtained on yellow card reports submitted to the CSM for the study drugs from the 79 participating practices during the study period in the form of anonymised individual patient prints. The reports were compared to the questionnaire responses.

2.7 Data analysis and statistical methods

Databases were set up for both the pilot study and the main study on SPSS for windows version 6.0 and version 9.0. After analysis of the pilot study data, some details of the database established were adjusted in order to improve its use for the main study. While SPSS was used for most data analysis, where this was not possible, Minitab for windows version 7 and version 12 were used.

The following analyses were carried out:

1. Patients' demographic details and general data on the medicines they were taking were studied using descriptive statistics. The Mann-Whitney U test was used for comparing median age or concomitant drugs between gender.
2. The number of reported symptoms and the number of concomitant drugs were further sub-grouped to enable relationships between these and other variables to be investigated.
3. The number of respondents using other drugs for the same indication as the study drugs and also those using other CNS drugs were calculated and relationships to other variables studied.
4. Relationships between the number of reported symptoms, age and number of concomitant drugs taken were investigated using Spearman's rank correlation.
5. All other relationships between variables obtained from the questionnaire were investigated using chi-square tests for association. Some data were regrouped, if necessary, for statistical analysis, e.g. age group, severity of symptoms, number of reported symptoms and number of concomitant drugs.
6. The ten most frequently reported symptoms for each drug in the questionnaires were compared to similar data for the study drugs obtained from the CSM, data

from PEM studies and symptoms recorded in medical notes, where available. The Z-test for two proportions was used for comparisons of the frequency of each individual symptom reported where sample sizes were sufficiently large.

7. The ten most frequently reported symptoms for each drug were compared within therapeutic categories using data from both the pilot and the main study. These symptoms were also compared to those obtained in published data. Comparisons were evaluated using the Z-test for two proportions for each individual symptom reported where sample sizes were sufficiently large.
8. Comparison of the classifications for causality for each individual symptom in 103 cases (53 tramadol and 50 venlafaxine) made by the research pharmacist and by an expert were investigated using the Kappa statistic.
9. An assessment of the ability of patients to accurately attribute symptoms to the drugs being studied was made by comparing the percentage of symptoms considered by the researcher to be probable or possible ADRs with those considered unlikely or not to be ADRs, using chi-square tests.

The 95% confidence interval or P-value at 0.05 was chosen to accept or reject the null hypotheses.

Chapter 3

Results and Discussion:

Pre-pilot and pilot study

3.1 Pre-pilot study

The pre-pilot study was carried out in July 1996. The purpose of the pre-pilot study was to develop a suitable questionnaire to be used in the pilot and main study. Both the closed and open questionnaires designed were sent to 14 patients by mail. One week after the questionnaires were sent, patients were contacted to arrange a home visit in order to ask their views on both questionnaires. There were five, five, three and one patients who had taken amitriptyline, trazodone, tramadol and moclobemide, respectively. Of these, 11 (79%) patients agreed to a home visit and nine (82%) reported at least one symptom since starting the drug. The patients' views on both types of questionnaire and their ability to complete the questionnaires are shown in Table 3.1. Based on this summary of patients' views, the closed questionnaire was chosen and questions relating to information about concomitant drugs and symptom severity were amended. In addition minor changes to the wording and layout of the questionnaire were made.

Table 3.1 Patients' views on and ability to complete the two different types of questionnaire

Patients' Views	No. of Patients (%)
1. Found no difficulty to fill in	11 (100%)
2. Closed questions were easier than open questions	9 (82%)
3. Open questions were easier than closed questions	1 (9%)
4. Both closed and opened questions were easy	1 (9%)
5. Questionnaire was quite long	1 (9%)
6. Unable to remember or difficult to remember start date	7 (64%)
7. Able to remember start date	4 (36%)
8. Gave more details in closed questions	9 (100%)*
9. Ticked a lot of boxes	3 (33%)*
10. Did not finish the open questions	2 (18%)
11. Did not tick " None" in the closed questions	3 (33%)*

* N = 9 (number of patients who reported at least one symptom)

3.2 Pilot study

Data collection for the pilot study was undertaken between October 1996 and September 1997. The developed questionnaire was customised for five established drugs; carbamazepine, sodium valproate, trazodone, doxepin and co-proxamol.

Patients who had been prescribed one of these drugs from three general practices in Aberdeen were sent the appropriate questionnaire.

3.2.1 Response rates and demographic data

There were 464 questionnaires sent to patients taking the five drugs which accounted for 173, 79 and 212 questionnaires sent to patients registered at the three practices. Of these, 207 questionnaires were returned (44.6%). The number of questionnaires sent and response rates for each drug are shown in Table 3.2. Of the total respondents, 35.3% were male and 64.7% were female (Table 3.3). The mean age ± SD of respondents was 54.5 ± 21.1 years, but the majority of patients were aged 60-79 years (35.3%) and 40-59 years (25.6%). The males had a median age of 58.0 years and the females 59.0 with no significant difference between males and females (Mann-Whitney U = 4599.5, P = 0.533). The number of respondents in each age group are presented in Figure 3.1.

Table 3.2 Number of questionnaires distributed and response rates for each drug

Drug	Number of questionnaires Sent	Number of respondents (%)
Carbamazepine	81	44 (54.3%)
Sodium valproate	52	25 (48.1%)
Trazodone	115	41 (35.7%)
Doxepin	105	52 (49.5%)
Co-proxamol	111	45 (40.5%)
Total	464	207 (44.6%)

Table 3.3 Number of respondents according to sex for each drug

	Number of respondents (%)					
	Car	**Val**	**Tra**	**Dox**	**Cop**	**Total**
Sex						
Male	21 (47.7%)	7 (28.0%)	15 (36.6%)	14 (26.9%)	16 (35.6%)	73 (35.3%)
Female	23 (52.3%)	18 (72.0%)	26 (63.4%)	38 (73.1%)	29 (64.4%)	134 (64.7%)

Car = carbamazepine, Val = sodium valproate, Tra = trazodone, Dox = doxepin, Cop = co-proxamol

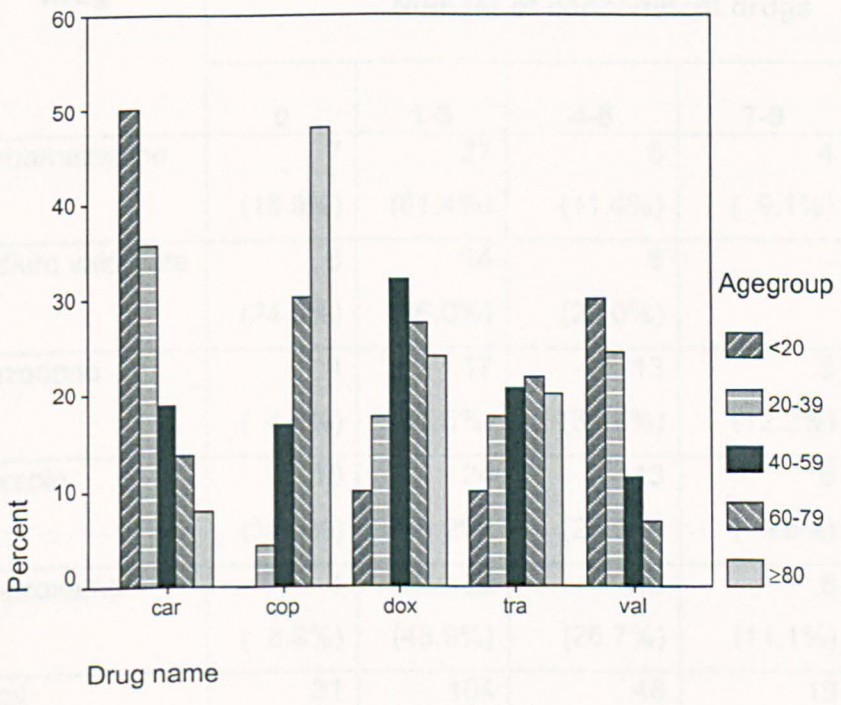

Figure 3.1 Age groups of respondents for each study drug

Of the total respondents, 50.2% and 23.2% were prescribed 1-3 and 4-6 concomitant drugs, respectively. The mean ± SD of number of concomitant drugs was 3.1 ± 2.6. There was no strong relationship between increasing age and number of concomitant

drugs (Spearman r = 0.289, P< 0.001). The number of concomitant drugs being taken by the respondents for each study drug are shown in Table 3.4. There were no significant differences between drugs in gender of respondents (χ^2 = 5.189, df = 4, P = 0.268) or in the numbers taking concomitant drugs (0-2 vs 3-4 vs 5-6 vs >6); (χ^2 = 17.039, df = 12, P = 0.148). Age group was however statistically different between drugs (χ^2 = 72.050, df = 12, P < 0.001). Respondents taking antiepileptics were younger, while those taking co-proxamol were the oldest.

Table 3.4 Number of concomitant drugs used by respondents taking study drugs

Drug	Number of respondents (%)					
	Number of concomitant drugs					Total
	0	1-3	4-6	7-9	≥10	
Carbamazepine	7 (15.9%)	27 (61.4%)	5 (11.4%)	4 (9.1%)	1 (2.3%)	44 (100%)
Sodium valproate	6 (24.0%)	14 (56.0%)	5 (20.0%)	-	-	25 (100%)
Trazodone	4 (4.9%)	17 (41.5%)	13 (31.7%)	5 (12.2%)	2 (4.9%)	41 (100%)
Doxepin	10 (19.2%)	24 (46.2%)	13 (25.0%)	5 (9.6%)	-	52 (100%)
Co-proxamol	4 (8.9%)	22 (48.9%)	12 (26.7%)	5 (11.1%)	2 (4.4%)	45 (100%)
Total	31 (15.0%)	104 (50.2%)	48 (23.2%)	19 (9.2%)	5 (2.4%)	207 (100%)

Of the total respondents prescribed carbamazepine, the most frequent indication for use was epilepsy (n=33, 75%), followed by manic depression (n=4, 11%), trigeminal neuralgia (n=5, 11%) and other neurological disorders (n=1, 2%), while almost all respondents were taking sodium valproate for epilepsy (n=24, 94%). Two respondents, one on each drug did not give the indication. For patients prescribed antidepressants, the indications for use of trazodone were depression (n= 28, 68%), anxiety (n=7,17%), sleeplessness (n=4,10%) and panic attack (n=1, 2%), while those for doxepin were depression (n= 31, 60%), anxiety (n=3, 6%), sleeplessness (n=13, 25%) and panic attack (n=1, 2%). The remaining four patients did not specify the indication. The most frequent indication for the use of co-proxamol was osteoarthritis (n= 17, 38%), followed by back pain (n= 7, 16%), unspecific pain (n= 6, 13%), other bone or muscle diseases (n= 5, 11%), rheumatoid arthritis (n=4, 9%) and spondylosis (n=4, 9%), headache (n=1, 2%) and degenerative bone or joint disease (n=1, 2%). Although 92 patients (44.4%) reported that they had been in hospital after starting the study drugs, none of them indicated that the admissions had been caused by these drugs.

3.2.2 Symptoms reported

The total number and frequency of symptoms reported for each drug are shown in Table 3.5. There was no strong relationship between number of reported symptoms and increasing age (Spearman $r = -0.158$, $P = 0.024$) or increasing number of concomitant drugs (Spearman $r = 0.275$, $P < 0.001$). The number of reported symptoms for each drug are presented in Figure 3.2 grouped for ease of interpretation (0-5 vs 6-10 vs 11-15 vs >15). There were no significant differences in the number of reported symptoms between drugs ($\chi^2 = 18.162$, df = 12, P-value = 0.111). However,

males reported significantly more symptoms than females (χ^2 = 15.024, df = 3, P = 0.002).

Table 3.5 Total number and frequency of symptoms reported for each drug

Drug (n)	No. of different symptoms reported	Total number of symptoms reported (median, range)
Carbamazepine (44)	73	283 (4.5, 0-22)
Sodium valproate (25)	79	269 (9.0, 0-41)
Doxepin (52)	79	310 (4.0, 0-24)
Trazodone (41)	87	452 (10.0, 0-34)
Co-proxamol (45)	77	300 (3.0, 0-51)

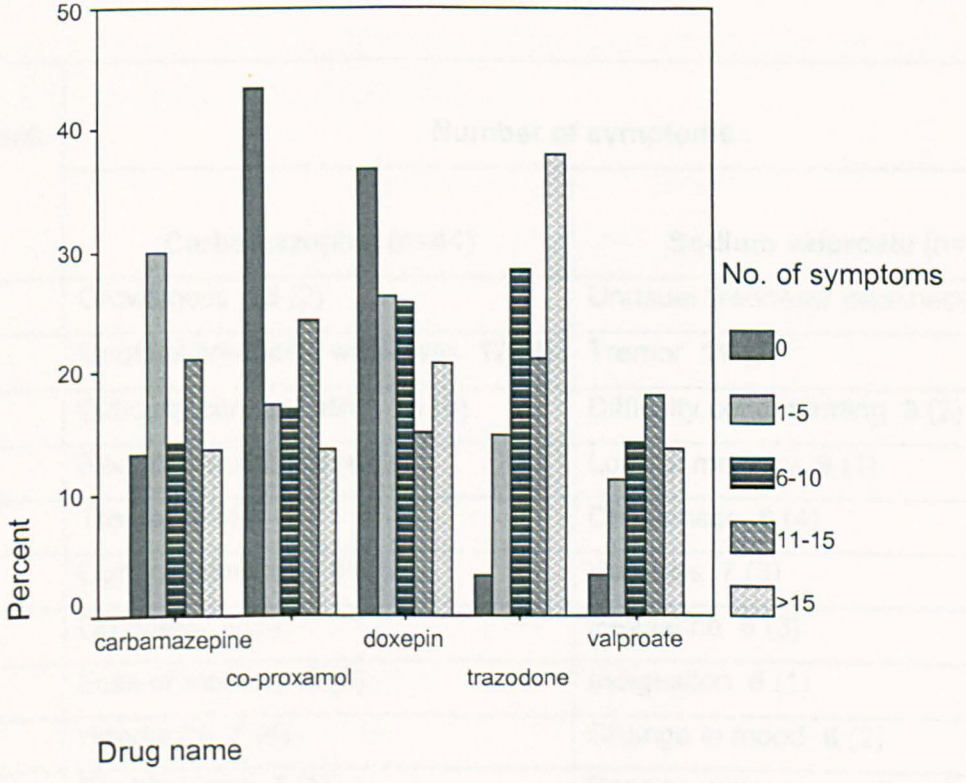

Figure 3.2 Grouped number of reported symptoms for each drug

Drowsiness, unusual tiredness/ weakness, dry mouth, dry mouth and constipation were the most frequently symptoms reported by patients prescribed carbamazepine, sodium valproate, trazodone, doxepin and co-proxamol, respectively. Appendix I shows frequency of each individual reported symptom categorised by body systems for each study drug. The ten most frequently reported symptoms for each drug along with the frequency with which these were recorded in the medical notes are shown in Tables 3.6, 3.7 and 3.8. Overall only 360 (22.3%) of total 1614 symptoms reported by patients were recorded by GPs. Sixty five (31.4%) and 17 (8.2%) of the total 207 respondents reported complete information in the questionnaire about concomitant drugs and disease states, respectively, compared with the records in their medical notes.

Table 3.6 The ten most frequently reported symptoms from the anticonvulsants by patient questionnaire (bold) and in medical notes ( )

Rank	Number of symptoms	
	Carbamazepine (n=44)	**Sodium valproate** (n=25)
1	Drowsiness **15** (2)	Unusual tiredness/ weakness **14** (5)
2	Unusual tiredness/ weakness **12** (4)	Tremor **11** (3)
3	Difficulty concentrating **10** (0)	Difficulty concentrating **9** (2)
4	Reduced vision **10** (4)	Loss of memory **9** (1)
5	Tremor **9** (1)	Drowsiness **8** (4)
6	Light-headedness **9** (1)	Hair loss **7** (3)
7	Dizziness **8** (3)	Headache **6** (3)
8	Loss of memory **8** (0)	Indigestion **6** (1)
9	Headache **7** (4)	Change in mood **6** (2)
10	Double vision **7** (1)	Passing water more often **6** (2) Anxiety **6** (2) Weight gain **6** (4)

Table 3.7 The ten most frequently reported symptoms from the antidepressants by patient questionnaire (bold) and in medical notes ( )

Rank	Number of symptoms	
	Trazodone (n=41)	**Doxepin** (n=52)
1	Dry mouth **20** (2)	Dry mouth **26** (2)
2	Anxiety **19** (12)	Indigestion **11** (3)
3	Drowsiness **17** (7)	Drowsiness **10** (2)
4	Light-headedness **16** (2)	Constipation **9** (2)
5	Unsteadiness on feet **14** (2)	Light-headedness **9** (2)
6	Unusual tiredness/ weakness **14**(5)	Excessive thirst **9** (0)
7	Difficulty concentrating **13** (3)	Unusual tiredness/ weakness **9** (1)
8	Constipation **13** (4)	Weight gain **9** (2)
9	Itching skin **12** (1)	Palpitations **9** (3)
10	Excessive thirst **12** (0)	Ringing in ears **9** (1)

Table 3.8 The ten most frequently reported symptoms from the analgesic by patient questionnaire (bold) and in medical notes ( )

Rank	Number of symptoms
	Co-proxamol (n=45)
1	Constipation **11** (1)
2	Itchy eyes **10** (2)
3	Dry mouth **10** (0)
4	Flushing **10** (2)
5	Itching skin **9** (3)
6	Change in finger nails **9** (0)
7	Increased sensitivity to cold **9** (0)
8	Dizziness **8** (1)
9	Excessive thirst **7** (0)
10	Unusual tiredness/ weakness **7** (2)

The most bothersome symptoms reported by patients taking carbamazepine were increased sleep (n = 4, 9%), loss of memory (n= 3, 7%), increased sweating (n= 2, 5%), dizziness (n=2, 5%), runny or stuffy nose (n=2, 5%), reduced vision (n=2, 5%) and tremor (n=2, 5%), while those taking sodium valproate were weight gain (n=4, 16%), loss of memory (n= 3,12%), unusual tiredness/ weakness (n=3, 12%) and difficulty concentrating (n= 2, 8%). Regarding patients taking the antidepressants, the most bothersome reported symptom for trazodone was unusual tiredness/ weakness (n=9, 22%), followed by increased sensitivity to cold (n=3, 7%), excessive thirst (n=3, 7%), difficulty concentrating (n=2, 5%) and weight gain (n=2, 5%), respectively, while the most bothersome reported symptom for doxepin was increased sleep (n=4, 8%), followed by increased sweating (n=3, 6%), reduction in sleep (n=2, 4%), change in mood (n=2, 4%), unusual tiredness/ weakness (n=2, 4%), diarrhoea (n=2, 4%), palpitations (n=2, 4%) and dry mouth (n=2, 4%), respectively. For patients taking the analgesic (co-proxamol), the five most bothersome symptoms reported included increased sweating (n=4, 9%), dry mouth (n=3, 7%), bone or joint pain (n=3, 7%), itching of skin (n=2, 4%) and difficulty concentrating (n=2, 4%).

There were 101 (48.8%) respondents who indicated they had reported some or all of these symptoms to their doctors. Respondents who reported more symptoms on the questionnaire were significantly more likely to have informed their doctors about the symptoms than those who reported less symptoms ($\chi^2 = 23.027$, df = 3, $P < 0.001$) as detailed in Table 3.9.

Table 3.9 Number of reported symptoms in relation to whether or not patients reported their symptoms to their doctors

Number of reported symptoms	Number of patients (%)		
	Whether patients informed their doctors of symptoms		Total*
	Yes	No	
≤ 5	28 (45.9%)	33 (54.1%)	61 (100%)
6-10	27 (87.1%)	4 (12.9%)	31 (100%)
11-15	25 (80.6%)	6 (19.4%)	31 (100%)
>15	21 (80.8%)	5 (19.2%)	26 (100%)

* Total number of valid cases =149

3.2.3 Severity of symptoms reported

Most respondents who rated the severity of their most bothersome symptoms rated them as moderate (28.0%) or severe (15.9%) (Table 3.10). There were no statistically significant associations between the severity of the reported symptoms in relation to the frequency of taking the drugs ($\chi^2 = 5.456$, df = 4, P = 0.244) or whether patients had informed their doctors about the symptoms ($\chi^2 = 5.815$, df = 2, P = 0.055) (see Table 3.11 and 3.12). In contrast, there was an association between symptom severity and the number of symptoms reported (Table 3.13). Patients rating their symptoms as severe were likely to report more symptoms than those who reported only mild symptoms ($\chi^2 = 23.459$, df = 6, P < 0.001). Severity of symptoms reported did not significantly associate with number of concomitant drugs ($\chi^2 = 4.426$, df = 6, P = 0.619) as presented in Figure 3.3.

Table 3.10 Severity ratings of the most bothersome symptoms reported by patients

Severity of symptoms	No. of respondents	%
Minimally	6	2.9
Mildly	19	9.2
Moderately	58	28.0
Severely	33	15.9
Very severely	15	7.2
Does not apply	46	22.2
Unspecified	30	14.5

Table 3.11 Severity of reported symptoms in relation to frequency of taking study drugs

Severity of symptoms	Number of patients (%)			
	Frequency of taking drugs (times/day)			Total*
	1	2	≥ 3	
Mild	11 (45.8%)	7 (29.2%)	6 (25.0%)	24 (100%)
Moderate	21 (37.5%)	16 (28.6%)	19 (33.9%)	56 (100%)
Severe	10 (21.3%)	17 (36.2%)	20 (42.6%)	47 (100%)

* Total number of valid cases = 127

Table 3.12 Severity of reported symptoms in relation to whether or not patients reported symptoms to their doctors

Severity of symptoms	Number of patients (%)		
	Whether patients informed their doctors of symptoms		Total*
	Yes	No	
Mild	13 (56.5%)	10 (43.5%)	23 (100%)
Moderate	38 (74.5%)	13 (25.5%)	51 (100%)
Severe	36 (83.7%)	7 (16.3%)	43 (100%)

* Total number of valid cases = 117

Table 3.13 Severity of symptoms reported in relation to number of reported symptoms

Severity of symptoms	Number of patients (%)				
	Number of reported symptoms				Total*
	≤ 5	6-10	11-15	>15	
Mild	14 (56.0%)	5 (20.0%)	3 (12.0%)	3 (12.0%)	25 (100%)
Moderate	19 (32.8%)	20 (34.5%)	11 (19.0%)	8 (13.8%)	58 (100%)
Severe	8 (16.7%)	7 (14.6%)	17 (35.4%)	16 (33.3%)	48 (100%)

* Total number of valid cases = 131

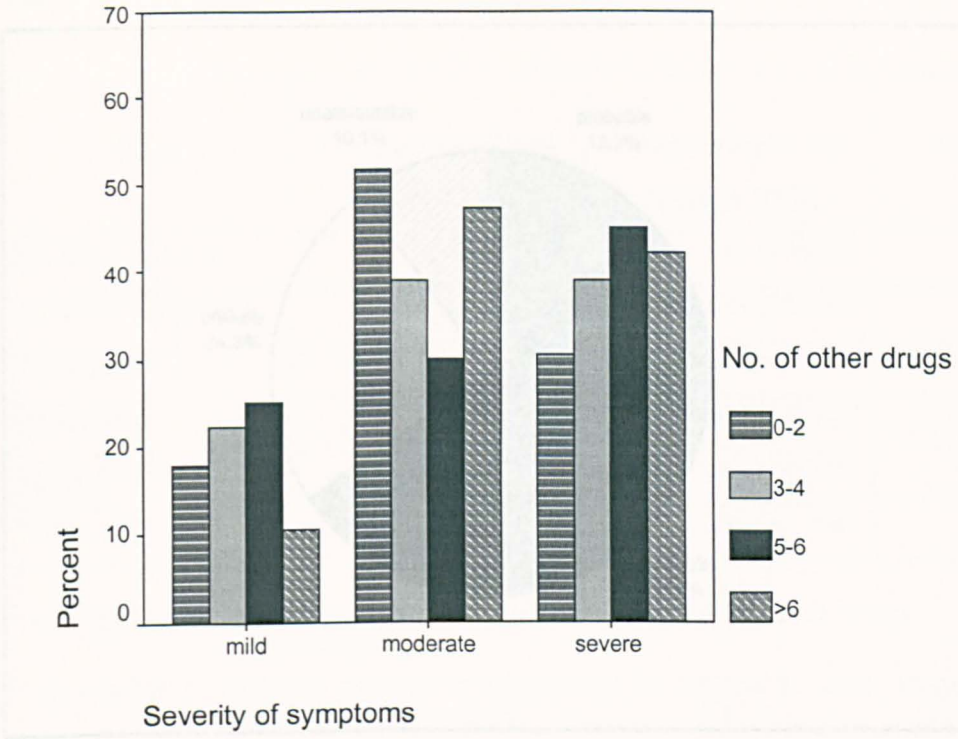

Figure 3.3 Severity of symptoms in relation to number of concomitant drugs

3.2.4 Patient attribution of symptoms to drugs

Approximately half of the symptoms reported by patients were classified by the researcher as being possibly caused by study drugs (n = 861), with a further 197 probably caused by study drugs. Three hundred and ninety three were classed as unlikely to be an ADR, and 163 were unattributable (Figure 3.4). The basis of the causal relationship was the classification of each reported symptom using eight criteria, the results of which are shown in Table 3.14. The classification was used to assess the accuracy of patient attribution of the side effects they reported (Table 3.15). Respondents were significantly more likely to report symptoms potentially caused by the study drug (probable/ possible) than those not likely to be caused by the study drug (unlikely/ unattributable) for each drug ($\chi^2 = 121.1$, df = 4, P <0.001).

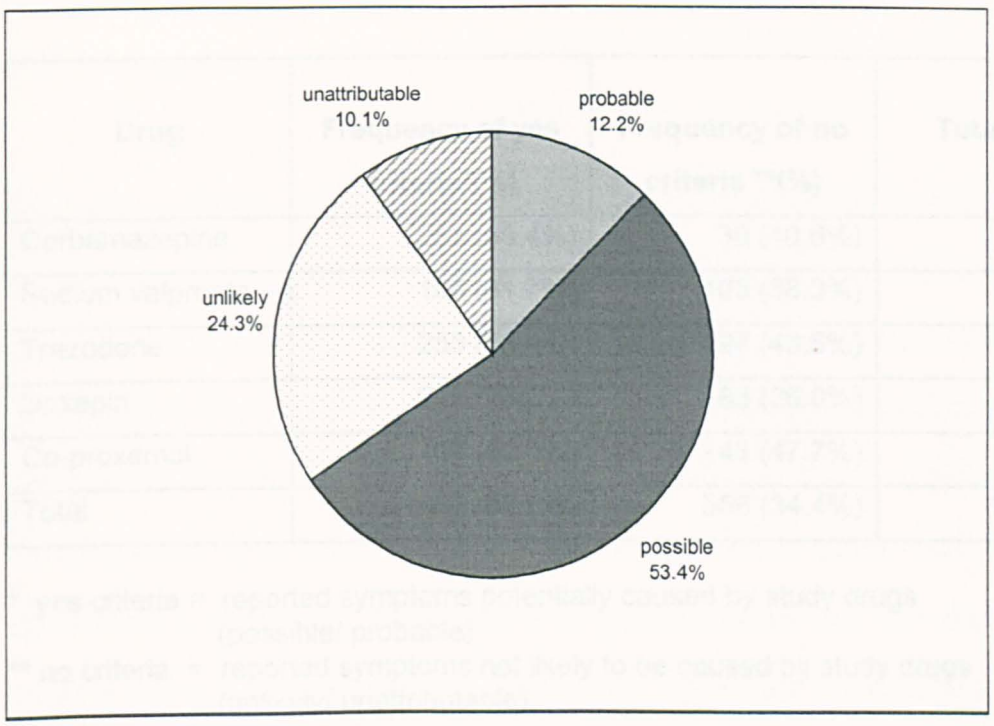

Figure 3.4 Classification of causal relationship of reported symptoms into four criteria

Table 3.14 Classification of reported symptoms classified into eight criteria for assessment of causal relationship

Causal relationship	Criteria	Total frequency of reported symptoms	
		No.	%
Probable ADRs	1	197	12.2
Possible ADRs	2	245	15.2
	3	198	12.3
	4	418	25.9
Subtotal		861	53.4
Unlikely ADRs	5	102	6.3
	6	181	11.2
	7	110	6.8
Subtotal		393	24.3
Unattributable ADRs	8	163	10.1
Total		1614	100

Table 3.15 Patient attribution accuracy of symptoms as side effects of drugs

Drug	Frequency of yes criteria*(%)	Frequency of no criteria **(%)	Total
Carbamazepine	253 (89.4%)	30 (10.6%)	283
Sodium valproate	166 (61.7%)	103 (38.3%)	269
Trazodone	255 (56.4%)	197 (43.6%)	452
Doxepin	227 (73.2%)	83 (26.8%)	310
Co-proxamol	157 (52.3%)	143 (47.7%)	300
Total	1058 (65.6%)	556 (34.4%)	1614

* yes criteria = reported symptoms potentially caused by study drugs (possible/ probable)
** no criteria = reported symptoms not likely to be caused by study drugs (unlikely/ unattributable)

As the number of reported symptoms increased, there was an increase in the proportion of patients reporting symptoms less likely to be caused by drugs and which were either classified as unlikely to be an ADR or unattributable (Table 3.16).

Table 3.16 Number of reported symptoms in relation to number of patients reporting at least one symptom classified as unlikely ADRs and unattributable

Number of reported symptoms	N	No. of patients reporting ≥1 unlikely ADR (%)	No. of patients reporting ≥1 unattributable symptoms (%)
≤ 5	110	26 (23.6%)	17 (15.5%)
6-10	35	23 (65.7%)	15 (42.9%)
11-15	33	26 (78.8%)	23 (67.9%)
>15	29	29 (100%)	27 (93.1%)

3.3 Discussion

3.3.1 Pre-pilot study

After asking patients' views on the two types of questionnaires and their ability to complete them, it was found that all eleven patients found them not difficult to fill in and neither caused any concern. Only one of the patients commented that the questionnaires were quite long. Nine felt that the list of symptoms was easier to complete than the open-ended questions. Also, patients gave more symptoms which they considered to be caused by their drugs using the closed questionnaire than the open-ended questionnaire. This finding is consistent with the work of Fisher et al. (1987c), Wallin and Sjovall (1981), Downing et al. (1970) and Ciccolunghi and Chaudrui (1975). They suggested that a checklist of symptoms could increase the reporting of symptoms which patients otherwise failed to recognise and the use of checklists appeared to detect a higher frequency of ADRs than spontaneous reporting. Rosenthal et al. (1996) also found that a standard questionnaire resulted in a higher prevalence of adverse effects than spontaneous reporting.

Furthermore, two patients did not finish completing the open questions. Therefore, the questionnaire containing the list of symptoms was selected for further development in this study. Rickels and Downing (1970) confirmed that specific questioning using checklists did not increase the number of drug-related symptoms through suggestion, although Borghi et al. (1984) found that a checklist seemed to suggest mild signs and symptoms to patients. However, the present study used a comprehensive list of symptoms for each body system to ask patients about all potential ADRs, not just those known to be related to the specific drugs in order to lessen the chance of bias and false positive responses.

Although open questions appeared to be more reliable for unexpected ADRs and to detect more serious ADRs than closed ones (Barber and Santanello, 1995; Wallin and Sjovall, 1981), the pilot study aimed to detect ADRs to well established drugs which have been available for a long period of time. It was considered unlikely that unexpected or rare ADRs would be detected within the small number of patients in the pilot study. Also, the main study for which the questionnaire was developed aimed to identify ADRs to black triangle drugs for which reports are requested of any ADRs related to the drugs, even known and minor ADRs. It was therefore considered likely that the checklist would help patients to report any symptoms which they had experienced.

Seven patients in the pre-pilot study were unable to remember the start date (month/ year) of all drugs taken exactly. Therefore some amendments were made to only ask about the start date of the study drug because this was considered important information which was required. As patients might have difficulty in recalling all of the start dates of the concomitant drugs taken, the modified questionnaire asked instead about the time relationship of the concomitant drugs with the study drug. The question thus asked whether the other drugs were started before or after the study drug and whether they had already stopped taking them or not. These questions were also emphasised by a sentence explaining that it was important for the researchers to know, therefore patients were requested to try to remember and fill in these questions. This question was also changed from the original which asked respondents to list all other drugs taken during the past month, to ask about drugs taken since starting the study drug. More details about the purpose of the questionnaire and repeated assurance that their medicine did not cause all the effects listed in the questionnaire were added in Part 2. Unlike the open-ended questionnaire, the checklist did not ask about the severity of symptoms in each body system, since this made it too long to fill

in. Instead, a question was asked about the severity of the most bothersome symptoms only. In each question in Part 2, the word 'complaints' was changed to the more specific 'side effects' in order to emphasise that patients should not tick other symptoms not caused by the study drug. Options for responses to the question concerning whether patients had told their doctors about their symptoms was modified from yes/ no to all/ some/ none in order to be applicable to all reported symptoms. Questions concerning symptoms appearing after stopping the study drug were also moved to become Part 3 and patients were asked to complete this part only if they had stopped taking the drug. This would reduce the time taken to complete the questionnaire for those who were still taking the drug.

3.3.2 Pilot study

Patients aged less than 16 were excluded from the present study as they were considered too young to complete the questionnaire and judge which symptoms may have been caused by study drug. Patients who lived in nursing homes were also excluded because they were presumed to be too ill to complete the questionnaire. The overall response rate of the pilot study was 44.6%. This appeared to be rather low despite sending a reminder to nonrespondents. However, a similar response rate (47.8%) was found by Ciccolunghi and Chaudri (1975) who studied patient-self reporting of symptoms via two types of questionnaire, open and closed questions. Bryant et al. (1990) found that the percentage of acceptance for the full sample of volunteers into a patient self-monitoring study was related to the amount of compensation given. Furthermore, a study to investigate effects of incentives on recruitment and response rate in community-based pharmacy practice research by Kennedy et al. (1999) found that significantly more customers who were provided free medicines from the participating pharmacies returned their questionnaires, compared

with those who were not provided with free medicines. It is possible, therefore, that compensation could have increased the response rate from patients in the present study. In relation to the types of drugs, the response rates from patients prescribed anticonvulsants (carbamazepine and sodium valproate) (51.9%) were slightly higher than from those taking antidepressants (trazodone and doxepin) (42.3%). This may be explained by patients with psychological problems being reluctant to complete the questionnaire. Another possible reason is that respondents taking antidepressants (majority were in the age group 60-79) were likely to be older than those taking anticonvulsants (majority were in the age group 20-39). However, when considering the overall response rate, patients aged 60-79 provided the highest response rate (35.3%). This may be because the respondents in this age group were less likely to be working and so have more time to complete the questionnaires. The present study found no relationship between increasing age and number of concomitant drugs. This finding is comparable to a study to monitor medication problems in the elderly by Pongwecharak (1998). On the contrary, Stewart et al. (1991) and Simons et al. (1992) found that older age was associated with the use of more prescribed medicines.

There was no statistical difference between the proportion of male and female respondents between study drugs. As a whole, two third of the respondents were female. This is in accordance with a study of patient self-monitoring by Fisher et al.(1993) in which approximately 75% of volunteer patients were female. On considering each drug separately, carbamazepine seemed to have a little higher proportion of male respondents (48%) than other drugs but there was no significant difference.

Half of the respondents were taking one to three concomitant drugs and around one quarter of them were taking four to six other drugs. The number of concomitant drugs

taken did not differ significantly between the study drugs, however slightly more respondents on carbamazepine (61%) took one to three concomitant drugs than was the case for other respondents.

Most patients were taking sodium valproate and carbamazepine for epilepsy, although a limited number of patients were taking carbamazepine for manic depression and trigeminal neuralgia. Also, most patients took co-proxamol for musculo-skeletal diseases. As would be expected, the majority of patients took antidepressants for depression (59, 63%) with a further 27 (29%) taking them for sleep difficulty and anxiety. This is consistent with a study by Fisher et al. (1993) in which it was found that 62% and 17% of patients had taken trazodone for depression and sleep difficulty, respectively. However, the present study had a higher proportion of patients taking trazodone for sleepless and anxiety (27%) than the study by Fisher et al. (1993) which may be due to differences in diagnosis or drug use between the USA and UK.

Males reported significantly more symptoms than females despite there being fewer male respondents. The present study did not find any positive relationship between increasing age and number of reported symptoms. This is in agreement with a study of the elderly over 65 using a questionnaire to report symptoms (Chrischilles et al., 1992), which found that increasing age appeared to be associated with a decreased tendency to report symptoms. It may be that the elderly under-report symptoms because of their perception that those symptoms were from the ageing process rather than being drug-related, although they may be more likely to experience ADRs than younger patients. However, a study which retrieved data from MEDLINE followed by selective reviews of all pertinent articles, indicated there was no relation between advancing patient age and the risk of adverse drug reactions (Gurwitz and Avorn, 1991). This is another possible reason for increasing age not being related to the

number of reported symptoms in this study. Alternatively, it could be due to alteration of ADR detection and reporting capacities of the elderly. In contrast, Bryant et al. (1991, 1992) found that those aged 50 or over were possibly better at discriminating probable ADRs from other types of adverse events than were younger patients. There was also no relationship between number of reported symptoms and number of concomitant drugs. This is in line with studies by Hallas et al. (1991), Pongwecharak (1998) and Fisher et al. (1993) which found no association between the number of prescribed drugs and the incidence of medication-related problems including ADRs.

The majority of respondents (over 50%) reported between one and five symptoms. However some reported very high numbers, up to 51. It is reasonable to assume that such respondents did experience a wide range of symptoms, however the possibility is high that many of these would be related to concomitant drugs or diseases, rather than to the study drug. Respondents taking trazodone reported the greatest number of different symptoms (87) and also the highest median per patient (10). A total of 79 different symptoms were reported to both sodium valproate and doxepin, despite there being more than twice as many doxepin-treated respondents than those receiving sodium valproate. A high median number of symptoms per patient was also found with sodium valproate (9). Carbamazepine on the other hand had the lowest number of different symptoms (73) and a much lower median per patient (4.5) than sodium valproate. This may suggest that carbamazepine is better tolerated than sodium valproate and doxepin better tolerated than trazodone. While respondents taking co-proxamol reported the lowest median number of symptoms (3), the highest number were also reported by a patient taking co-proxamol (51).

Some of the top ten symptoms reported may have been associated with patients' illness rather than the drugs taken, for example, anxiety and difficulty concentrating for

trazodone, unusual tiredness/ weakness and decrease in sexual desire for doxepin, loss of memory for carbamazepine and sodium valproate. However, no patients taking the antidepressants who cited anxiety as a symptom also gave it as the indication. It is possible that some patients tended to report symptoms which were due to their illness as these symptoms were likely to interfere their lifestyle or be particularly bothersome, which led patients to report these symptoms in high percentages. Also, patients may have found it was difficult to judge whether these symptoms were caused by their illness or the study drug.

The ten symptoms most frequently reported by patients for each drug were as expected except indigestion for doxepin, anxiety for trazodone, and itchy or irritated eyes and change in finger nails for co-proxamol. These symptoms could have been caused by patients' disease states or be ADRs of concomitant drugs. For doxepin, of the total 11 symptoms reported as indigestion, five (45%) were attributable to only concomitant drugs, two (18%) were attributable to only patients' illness and four (36%) were attributable to both illness and concomitant drugs. For trazodone, of the total 19 symptoms reported as anxiety, seven (37%) were attributable to only patients' illness and 11 (58%) were attributable to both illness and concomitant drugs taken. For co-proxamol, of the total ten symptoms reported as itchy or irritated eyes, four (40%) were attributable to only concomitant drugs taken, two (20%) were attributable to only patients' illness and four (40%) were unattributable, while all nine of the symptoms reported as change in finger nails were unattributable.

Many of the symptoms cited as being most bothersome by respondents were also among those most frequently reported. This was particularly evident in the case of carbamazepine, for which five of the ten most frequently reported symptoms were also stated to be most bothersome, particularly drowsiness and memory loss. Three of the

four most often cited bothersome symptoms for sodium valproate were also among the top four most frequently reported, including unusual tiredness/ weakness. Weight gain with sodium valproate was the most frequently cited bothersome symptom, by four (16%) respondents, which suggests that most patients who do gain weight are concerned by it. Three of the top ten symptoms for trazodone were among those stated to be most bothersome, with unusual tiredness being cited most frequently. However this was the only one of the top ten symptoms reported with doxepin which was regarded as bothersome. Dry mouth and itchy skin were the only two symptoms reported frequently to co-proxamol which were cited as bothersome. Unusual tiredness/ weakness and drowsiness were therefore both reported frequently and were considered bothersome by many respondents taking anticonvulsants and antidepressants. While these could be symptoms of the disease states present in the patients, rather than adverse effects, they are nonetheless likely to interfere with lifestyle and it is perhaps not surprising that they were cited frequently.

Data from Drugdex Drug Evaluation Monographs (1998), ABPI Compendium of Datasheets and Summaries of Product Characteristics (The Association of the British Pharmaceutical Industry, 1998) and Handbook of Clinical Drug Data (Knoben and Anderson, 1994) showed that vertigo, ataxia, drowsiness, unsteadiness on feet and dizziness are relatively common side effects of carbamazepine which were also found in the ten most frequently reported symptoms of this study. However, the commonest side effects of sodium valproate are nausea, diarrhoea, abdominal cramp and indigestion of which only indigestion appeared in the top ten, most likely because these symptoms often occur during the initiation of therapy. This study asked patients to report any symptoms experienced during the previous 12 months at the time that they received the questionnaire, so those gastrointestinal symptoms may have already disappeared by the time of the study. For trazodone, the common side effects include

drowsiness, fatigue, dizziness, hypotension, nausea and vomiting. Most of these were also found to be the top ten symptoms reported in the present study, except nausea, vomiting and dizziness. Again nausea and vomiting tend to disappear on continued treatment. Dizziness was presumably difficult to differentiate from light-headedness and unsteadiness on feet which were also two of the top ten symptoms reported in this study. For doxepin, drowsiness, anticholinergic side effects, especially dry mouth and constipation, and hypotension are relatively common side effects. All were included in the top ten symptoms reported. For co-proxamol, the common side effects were dizziness, sedation and nausea and vomiting, but only dizziness was one of the ten most frequently reported symptoms in this study. Again it is possible that tolerance had developed to nausea, vomiting and sedation or that these symptoms already disappeared at the time of the study. Constipation was the commonest symptom reported in this study. This may be because tolerance does not develop to constipation and there are probably actually a large of number of patients taking co-proxamol in the community who suffer from this symptom. Therefore, despite it being a minor symptom, it was consequently reported frequently in the questionnaires.

For trazodone, the five most frequently reported symptoms including dry mouth, anxiety, drowsiness, light-headedness and unsteadiness on feet were the same as a previous study by patient self-monitoring using telephone interviews (Fisher et al., 1993), although the frequency found in the present study was higher. Using questionnaires to identify possible ADRs as opposed to telephone interviews after spontaneous patient-reporting may pick up more potential ADRs.

Respondents were asked to rate the severity of their most bothersome symptoms into one of six categories. The results showed that subjective severity ratings for these symptoms tended to be more than merely minimal or mild, which is compatible with

the study by Fisher et al. (1993). The most frequent severity reported was moderately (28%) followed by severely (16%), while minimal severity was cited least often (3%). A number of patients did not report any side effects at all and they ticked all lists of side effects in each body system as none. Also some who did report symptoms may not have felt the symptoms bothered them and either did not provide a severity rating or selected 'does not apply'. There thus appeared to be a clear division between those who reported no or minimal symptoms and those who identified many symptoms, at least some of which they regarded as bothersome to a moderate or severe degree. This is supported by the strong association found between severity rating and number of symptoms reported.

This shows that patients were much more likely to report in questionnaires adverse effects that were particularly more subjectively severe and bothersome to them which is in agreement with studies by Fisher et al., (1995) and Fisher (1995). However the lack of a statistically significant relationship between severity and informing their doctor is surprising, this may be due to small numbers, since in fact 84% of patients rating symptoms as severe did report these to their doctor. Conversely there were similar numbers of patients reporting mild symptoms to their doctor as did not do so. There was however a strong tendency for patients identifying more than five symptoms to report these to their doctor. A few patients, despite claiming to experience symptoms which were severe or moderately severe, clearly did not view them as being sufficiently important to inform the doctor about them. Perhaps this is due to the opportunity presented by the questionnaire in contrast to the need to be pro-active in informing a doctor.

The failure of many patients to report all symptoms to their GP could have contributed to most of these not being recorded in medical notes. When the symptoms reported by

patient questionnaire were compared with those recorded in the medical notes of the same patient, it was revealed that the frequency with which symptoms reported by patients were recorded in the medical notes was extremely low. Overall only 22% of total symptoms reported were recorded, even for symptoms well known to be caused by drugs which patients were prescribed. This finding supports the under-reporting of ADRs by doctors to the CSM. Further explanations for infrequent records in the medical notes could include doctors not being concerned about any minor and well-established side effects reported by patients or having limited time to record those reported symptoms. In many cases the symptoms may not have been related to the study drugs, instead being caused by patients' disease states or concomitant drugs. The doctors may also feel unsure about attributing reported symptoms definitely to a particular drug. There have been several studies investigating the reasons for under-reporting of ADRs to authorities (Inman and Weber, 1986; Belton et al., 1995; Bateman et al., 1992; Inman and Pearce 1993; Randhawa et al., 1987; Smith et al., 1996; Scott et al., 1987; Rosenbaum et al., 1990; Rogers et al., 1988; Generali et al., 1995). Those reasons included uncertainty about whether the drug caused the reaction, lack of time, lethargy resulting in unwillingness to notify the ADRs, guilt because of unintentional harm caused to patients, complacency about the safety of approved drugs, poor knowledge and attitudes, well-known reactions to established drugs and unawareness of ADRs. Thus similar reasons could explain lack of recording as well.

The causal relationships produced by classifying the reported symptoms into eight criteria showed that by far the greatest proportion (26%) fell into category 4, which stated that the symptom could be caused by the study drug, concomitant drugs and diseases. A further 27% of symptoms could have been caused by the study drug and either concomitant drugs (category 2) or diseases (category 3). Therefore for over half

the symptoms reported the possibility existed that the study drug could have been the cause, but there was no way of ascertaining this any more clearly. Symptoms falling into these three categories were grouped together as possibly being caused by the study drug. This illustrates the difficulties associated with patients' self-reporting, since it becomes impossible to attribute symptoms to particular drugs without details of time relationships. However there are similar difficulties in attribution in any situation, as evidenced by this being cited as a reason for under-reporting to regulatory authorities (Bateman et al., 1992; Randhawa et al., 1987; Scott et al., 1987; Generali et al., 1995).

In 12% of reported symptoms which were known to have been previously reported to the study drugs, there were no other obvious causes among concomitant drugs or diseases (category 1), therefore these were classed as probable ADRs. Combining both possible and probable ADRs gave a total of 65% of reported symptoms which could have been due to the study drugs. This suggests that patients were reporting with a useful degree of accuracy. Indeed for all five drugs in this pilot study, patients were more likely to report probable or possible ADRs than other symptoms which were unlikely to be ADRs (categories 5,6 and 7) or were unknown to be associated with any drugs being taken or disease states (category 8). This degree of attribution by patients is similar to that found by Fisher et al. (1994). These workers also found that discrimination was better when patients reported adverse events spontaneously rather than through systematic enquiry by interview. A further study using an interview to determine patients' ability to accurately discriminate possible ADRs from other symptoms also found similar attribution rates (almost 70%) (Solovitz et al. 1987). The comparable degree of attribution found in the present study using a systematic questionnaire could therefore be considered to be better than may have been expected.

A surprisingly high number of symptoms reported (10%) could not be attributed to any of the patients' drugs or disease states. This does suggest that patients may have over-reported, as was found from the results of the study by Borghi et al. (1984). There is also a strong possibility of bias arising from the likely higher probability of those who returned questionnaires having symptoms to report. The over-reporting may have been by only a proportion of respondents, as those reporting more symptoms were more likely to report symptoms not known to be caused by the study drugs. This suggests that patients who reported more symptoms seemed to be worse discriminators than those who reported less symptoms.

Chapter 4

Results and Discussion:

Main study

General practices in Grampian were approached to ask for their co-operation with this study. Eighty one percent of the total of 97 medical practices agreed to allow their patients to be included in the study. A total of 2307 postal questionnaires with pre-paid envelopes were distributed to patients who were prescribed one of nine black triangle drugs during January – March 1997.

4.1 Results

4.1.1 Response rates and demographic data

There was a total of 924 questionnaires returned which accounted for an overall response rate of 40.1%. However, the number of respondents who returned valid questionnaires was 837, 36.3% of the total questionnaires sent to patients. Table 4.1 lists the number of questionnaires sent to patients and response rates for each study drug. The highest response rates (59.1%) were found in patients taking gabapentin, topiramate (56.5%) and lamotrigine (45.0%) although the numbers were small. The greatest number of questionnaires were issued and returned from patients prescribed tramadol and venlafaxine, since these drugs were prescribed most frequently. Of the total respondents, 33.2% were male, 66.2% were female, 0.6% did not specify. The greatest proportion of females were found in those prescribed antidepressants (n = 269, 69.7%), followed by those prescribed analgesics (n = 232, 65.9%) and those prescribed anticonvulsants (n = 53, 53.5%). The mean ± SD age of the respondents

was 50.5 ± 17.2 years, with the majority of respondents falling into the 40-59 (38.0%) and 20-39 (28.2%) age groups. Characteristics of the respondents are presented in Table 4.2. The males had a median age of 49.0 years and the females 48.0 years with no significant difference between males and females (Mann-Whitney U = 74261.5, P = 0.800).

Of the total respondents, 50.2% and 25.7% were prescribed 1-3 and 4-6 concomitant drugs, respectively. The mean ± SD of number of concomitant drugs was 3.0 ± 2.2. The number of respondents taking concomitant drugs is shown in Table 4.3. Females were taking significantly more concomitant drugs (median 3.0, range 0-16) than males (median 2.0, range 0-16); (Mann-Whitney U = 53583.5, P = 0.008), however the relationship between increasing age and number of concomitant drugs was not strong (Spearman r = 0.307, P < 0.001).

Table 4.1 Number of respondents and response rates

Drug	No. of questionnaires sent	No. of valid respondents	Response rate (%)
Citalopram	132	43	32.6
Fentanyl patch	64	8	12.5
Gabapentin	115	68	59.1
Lamotrigine	40	18	45.0
Moclobemide	48	16	33.3
Nefazodone	204	64	31.4
Topiramate	23	13	56.5
Tramadol	1048	344	32.8
Venlafaxine	633	263	41.5
Total	2307	837	36.3

Table 4.2 Number of respondents according to sex and age groups

	Number of respondents	%
Sex		
Male	278	33.2
Female	554	66.2
not specified	5	0.6
Age group		
< 20	9	1.1
20-39	236	28.2
40-59	318	38.0
60-79	212	25.3
≥ 80	47	5.6
not specified	15	1.8
Total	837	100

Table 4.3 Number of respondents according to number of concomitant drugs

Number of concomitant drugs	Number of respondents	%
0	53	6.3
1-3	420	50.2
4-6	215	25.7
7-9	48	5.7
≥10	8	1.0
not specified	93	11.1
Total	837	100

4.1.2 Symptoms reported

Of the total 837 respondents, 742 (88.6%) reported at least one symptom. The total number of symptoms reported was 7016 and the median per patient was 6.0 (range 0-71). Patients prescribed tramadol and venlafaxine reported more different symptoms and a higher number of symptoms than those prescribed other drugs, while those prescribed fentanyl patch had the greatest median of number of symptoms reported, followed by nefazodone, venlafaxine and moclobemide, respectively (Table 4.4). The number of reported symptoms were grouped into five categories (≤5, 6-10, 11-15, 16-20 and ≥20). Both males and females reported less than six symptoms with the highest frequency. The number of symptoms reported showed no relationship to sex (χ^2 = 2.722, df = 4, P = 0.605), age (Spearman r = - 0.089, P = 0.2152 for grouped data) or the number of concomitant drugs being taken (Spearman r = 0.026, P = 0.414 for grouped data) (Table 4.5, Table 4.6 and Table 4.7). The greatest proportion of respondents had been taking one of the drugs under study for between 181 to 360 days as shown in Table 4.8. Duration of therapy did not appear to influence the number of reported symptoms (χ^2 = 20.583, df = 16, P = 0.195).

Table 4.4 Total number and frequency of symptoms reported for each drug

Drug (n)	No. of different symptoms reported	Total number of symptoms reported (median, range)
Citalopram (43)	78	358 (5.0, 0-37)
Fentanyl patch (8)	47	94 (12.5, 2-24)
Gabapentin (68)	77	575 (5.5, 0-37)
Lamotrigine (18)	46	117 (5.0, 0-17)
Moclobemide (16)	52	103 (6.5, 0-16)
Nefazodone (64)	85	677 (8.5, 0-39)
Topiramate (13)	41	59 (3.0, 0-12)
Tramadol (344)	92	2333 (4.5, 0-51)
Venlafaxine (263)	97	2700 (7.0, 0-71)

Table 4.5 Number of reported symptoms compared to sex of respondents

Sex	Number of patients (%)					
	Number of reported symptoms					Total
	≤5	6-10	11-15	16-20	>20	
Male	133 (47.8%)	64 (23.0%)	35 (12.6%)	24 (8.6%)	22 (7.9%)	278 (100%)
Female	273 (49.3%)	105 (19.0%)	75 (13.5%)	45 (8.1%)	56 (10.1%)	554 (100%)
Not specified	2 (40.0%)	2 (40.0%)	-	-	1 (20.0%)	5 (100%)

Table 4.6 Number of reported symptoms compared to age group

Age group	Number of patients (%)					
	Number of reported symptoms					Total*
	≤5	6-10	11-15	16-20	>20	
≤25	26 (48.1%)	10 (18.5%)	6 (11.1%)	6 (11.1%)	6 (11.1%)	54 (100%)
26-50	178 (45.3%)	84 (21.4%)	57 (14.5%)	36 (9.2%)	38 (9.7%)	393 (100%)
51-75	143 (48.6%)	62 (21.1%)	40 (13.6%)	22 (7.5%)	27 (9.2%)	294 (100%)
≥75	55 (67.9%)	10 (12.3%)	6 (7.4%)	4 (4.9%)	6 (7.4%)	81 (100%)

* Total number of valid cases = 822

Table 4.7 Number of reported symptoms compared to number of concomitant drugs

Number of concomitant drugs	Number of patients (%)					
	Number of reported symptoms					Total*
	≤5	6-10	11-15	16-20	>20	
0-2	174 (47.8%)	84 (23.1%)	50 (13.7%)	24 (6.6%)	32 (8.8%)	364 (100%)
2-4	92 (46.2%)	40 (20.1%)	31 (15.6%)	18 (9.0%)	18 (9.0%)	199 (100%)
4-6	67 (53.6%)	18 (14.4%)	15 (12.0%)	12 (9.6%)	13 (10.4%)	125 (100%)
>6	26 (46.4%)	9 (16.1%)	5 (8.9%)	7 (12.5%)	9 (16.1%)	56 (100%)

* Total number of valid cases = 744

Table 4.8 Number of reported symptoms compared to duration of therapy

Duration of therapy (days)	Number of patients (%)					
	Number of reported symptoms					Total*
	≤5	6-10	11-15	16-20	>20	
1-180	81 (56.6%)	24 (16.8%)	21 (14.7%)	8 (5.6%)	9 (6.3%)	143 (100%)
181-360	106 (49.1%)	51 (23.6%)	28 (13.0%)	17 (7.9%)	14 (6.5%)	216 (100%)
361-540	61 (38.9%)	38 (24.2%)	25 (15.9%)	13 (8.3%)	20 (12.7%)	157 (100%)
541-720	41 (46.6%)	16 (18.2%)	15 (17.0%)	6 (6.8%)	10 (11.4%)	88 (100%)
>720	38 (42.2%)	19 (21.1%)	10 (11.1%)	10 (11.1%)	13 (14.4%)	90 (100%)

* Total number of valid cases = 694

The majority of the respondents had taken the study drugs once a day (57.0%). There was no significant relationship between the frequency of dosing and the number of reported symptoms ($\chi^2 = 5.109$, df = 8, P = 0.746) as presented in Table 4.9. Thirty nine percent of the respondents were taking other drugs with the same indication as the study drug and 48.7% of respondents were taking other CNS drugs. Concomitant use of further drugs for the same indication as the study drug did not appear to affect the number of reported symptoms ($\chi^2 = 2.036$, df = 4, P = 0.729) (Table 4.10). However, patients taking any other CNS drug were likely to report significantly more symptoms than those not taking other CNS drugs as shown in Table 4.11 ($\chi^2 = 20.069$, df = 4, $P < 0.001$). Appendix J lists frequency of each individual reported symptom categorised by body systems for each study drug.

Table 4.9 Number of reported symptoms compared to frequency of drug use

Frequency of taking drugs (times/day)	Number of patients (%)					
	Number of reported symptoms					Total*
	≤5	6-10	11-15	16-20	>20	
1	40 (50.3%)	100 (21.0%)	57 (11.9%)	37 (7.8%)	43 (9.0%)	477 (100%)
2	117 (47.0%)	50 (20.1%)	37 (14.9%)	21 (8.4%)	24 (9.6%)	249 (100%)
≥3	16 (40.0%)	11 (27.5%)	8 (20.0%)	2 (5.0%)	3 (7.5%)	40 (100%)

* Total number of valid cases = 766

Table 4.10 Presence of other drugs with the same indication in relation to number of reported symptoms

Presence of other drugs with the same indication	Number of patients (%)					
	Number of reported symptoms					Total*
	≤5	6-10	11-15	16-20	>20	
No	149 (45.7%)	68 (20.9%)	43 (13.2%)	28 (8.6%)	38 (11.7%)	326 (100%)
Yes	183 (49.3%)	73 (19.7%)	52 (14.0%)	30 (8.1%)	33 (8.9%)	371 (100%)

* Total number of valid cases = 697

Table 4.11 Presence of other CNS drugs in relation to number of reported symptoms

Presence of other CNS drugs	Number of patients (%)					
	Number of reported symptoms					Total*
	≤5	6-10	11-15	16-20	>20	
No	208 (51.0%)	86 (21.1%)	60 (14.7%)	28 (6.9%)	26 (6.4%)	408 (100%)
Yes	124 (42.9%)	55 (19.0%)	35 (12.1%)	30 (10.4%)	45 (15.6%)	289 (100%)

* Total number of valid cases = 697

4.1.3 Severity of symptoms reported

The majority of respondents rated the severity of their most bothersome symptoms reported as moderate (27.6%) and severe (21.5%) (Figure 4.1). Although no significant association was found between the total number of concomitant drugs and symptom severity (χ^2 = 12.776, df = 8, P = 0.120), it can be seen from Figure 4.2 that all respondents taking ten or more concomitant drugs rated their symptoms as moderate or severe, while the majority of those taking between four and nine other drugs rated symptoms as severe.

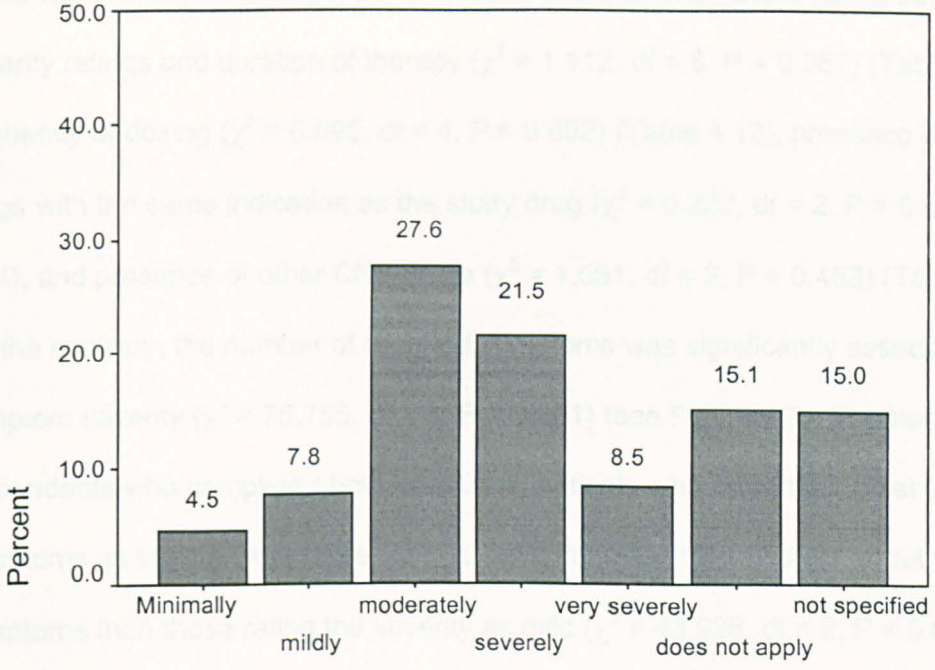

Figure 4.1 Classification of severity of most bothersome symptoms reported

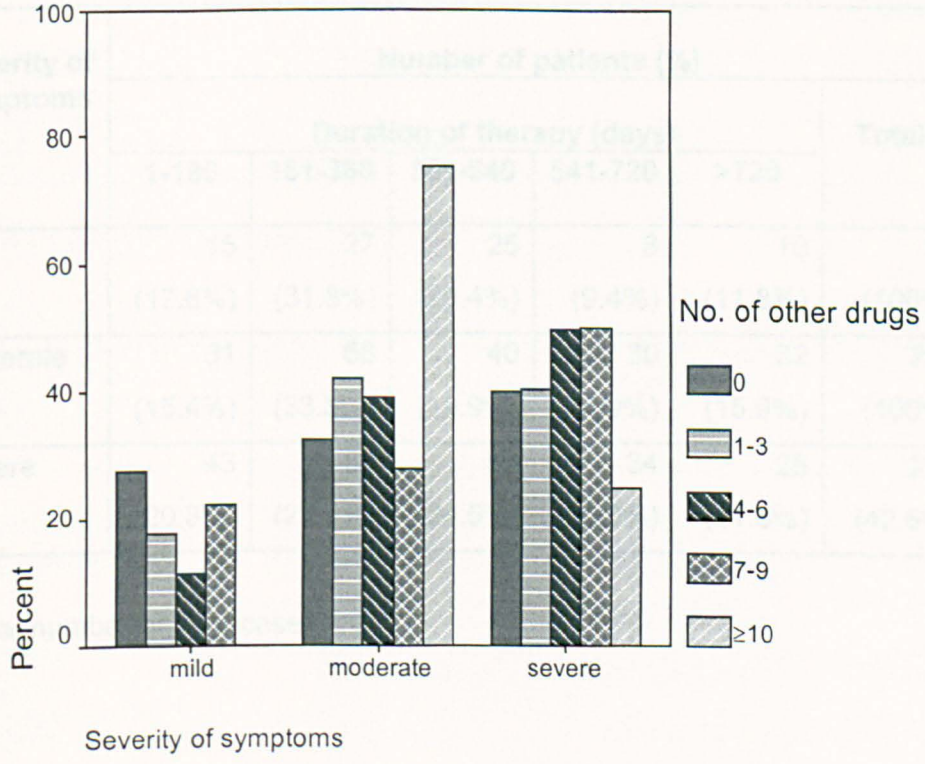

Figure 4.2 Severity of most bothersome symptoms in relation to number of concomitant drugs

There were no significant associations found in those who gave a rating between the severity ratings and duration of therapy (χ^2 = 1.112, df = 8, P = 0.367) (Table 4.12), frequency of dosing (χ^2 = 8.695, df = 4, P = 0.892) (Table 4.13), presence of other drugs with the same indication as the study drug (χ^2 = 0.232, df = 2, P = 0.891) (Table 4.14), and presence of other CNS drugs (χ^2 = 1.561, df = 2, P = 0.458) (Table 4.15). On the contrary, the number of reported symptoms was significantly associated with symptom severity (χ^2 = 75.765, df = 8, P < 0.001) (see Figure 4.3). For those respondents who completed both questions, patients who rated their most bothersome symptoms as severe were more likely to have informed their doctors about these symptoms than those rating the severity as mild (χ^2 = 43.926, df = 2, P < 0.001) (Table 4.16).

Table 4.12 Severity of symptoms in relation to duration of therapy

Severity of symptoms	Number of patients (%)					
	Duration of therapy (days)					Total*
	1-180	181-360	361-540	541-720	>720	
Mild	15 (17.6%)	27 (31.8%)	25 (29.4%)	8 (9.4%)	10 (11.8%)	85 (100%)
Moderate	31 (15.4%)	68 (33.8%)	40 (19.9%)	30 (14.9%)	32 (15.9%)	201 (100%)
Severe	43 (20.3%)	58 (27.4%)	52 (24.5%)	34 (16.0%)	25 (11.8%)	212 (42.6%)

* Total number of valid cases = 498

Table 4.13 Severity of symptoms in relation to frequency of taking study drugs

Severity of symptoms	Number of patients (%)			
	Frequency of taking drugs (times/day)			Total*
	1	2	≥3	
Mild	61 (62.2%)	31 (31.6%)	6 (6.1%)	98 (100%)
Moderate	134 (63.5%)	68 (32.2%)	9 (4.3%)	211 (100%)
Severe	138 (60.3%)	77 (33.6%)	14 (6.1%)	229 (100%)

* Total number of valid cases = 538

Table 4.14 Severity of symptoms in relation to whether presence of other drugs with the same indication

Severity of symptoms	Number of patients (%)		
	Presence of other drugs with the same indication		Total*
	No	Yes	
Mild	35 (46.1%)	41 (53.9%)	76 (100%)
Moderate	96 (49.2%)	99 (50.8%)	195 (100%)
Severe	103 (48.8%)	108 (51.2%)	211 (100%)

* Total number of valid cases = 482

Table 4.15 Severity of symptoms in relation to whether presence of other CNS drugs

Severity of symptoms	Number of patients (%)		
	Presence of other CNS drugs		Total*
	No	Yes	
Mild	48 (63.2%)	28 (36.8%)	76 (100%)
Moderate	113 (57.9%)	82 (42.1%)	195 (40.5%)
Severe	116 (55.0%)	95 (45.0%)	211 (100%)

* Total number of valid cases = 482

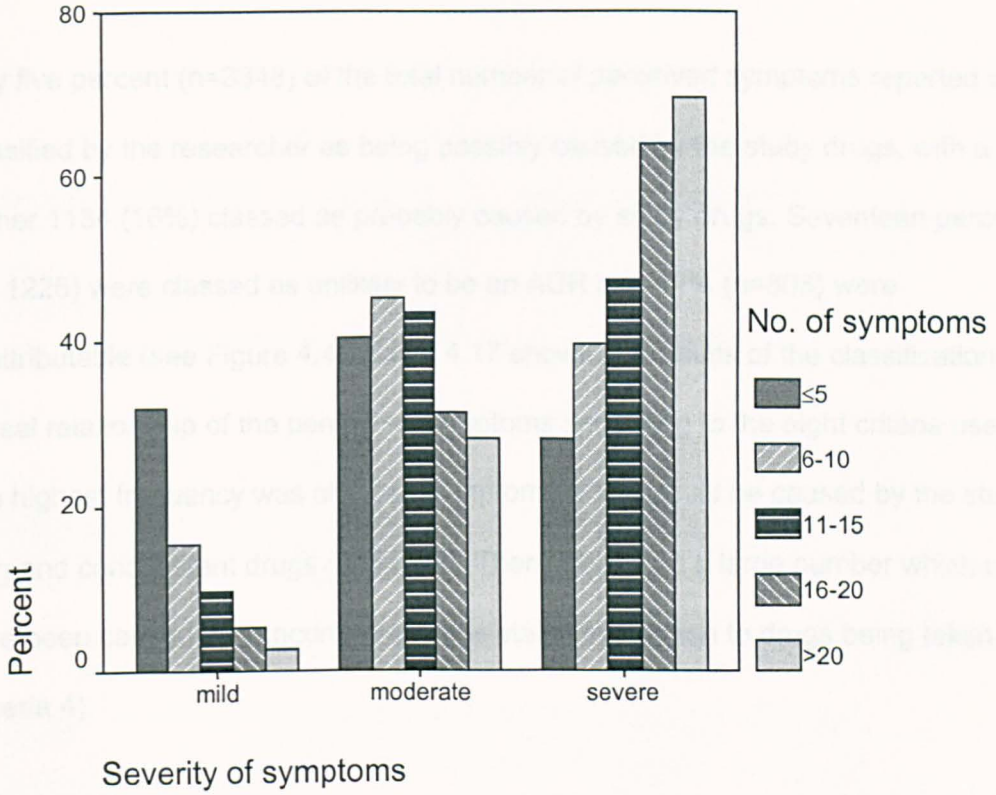

Figure 4.3 Severity of most bothersome symptoms in relation to number of reported symptoms

Table 4.16 Severity of reported symptoms in relation to whether or not patients reported symptoms to their doctors

Severity of symptoms	Number of patients (%)		
	Whether patients informed their doctors of symptoms		Total*
	Yes	No	
Mild	31 (52.5%)	28 (47.5%)	59 (100%)
Moderate	151 (76.3%)	47 (23.7%)	198 (100%)
Severe	186 (87.7%)	26 (12.2%)	212 (100%)

* Total number of valid cases = 469

4.1.4 Patient attribution of symptoms to drugs

Fifty five percent (n=3848) of the total number of perceived symptoms reported were classified by the researcher as being possibly caused by the study drugs, with a further 1134 (16%) classed as probably caused by study drugs. Seventeen percent (n= 1226) were classed as unlikely to be an ADR and 12% (n=808) were unattributable (see Figure 4.4). Table 4.17 shows the results of the classification for causal relationship of the perceived symptoms according to the eight criteria used. The highest frequency was of those symptoms which could be caused by the study drug and concomitant drugs (criteria 2). There were also a large number which could have been caused by concurrent disease states in addition to drugs being taken (criteria 4).

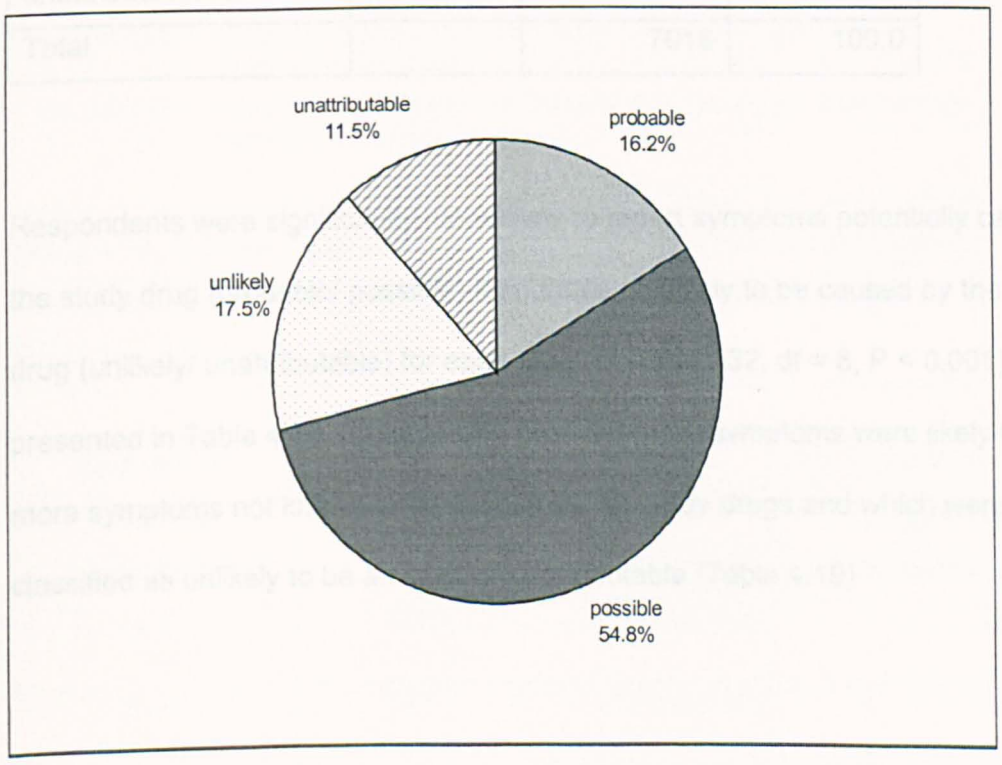

Figure 4.4 Classification of causal relationship of reported symptoms into four criteria

Table 4.17 Number of total frequency of reported symptoms classified into eight criteria according to causal relationship

Causal relationship	Criteria	Total frequency of reported symptoms	
		No.	%
probable ADRs	1	1134	16.2
possible ADRs	2	1619	23.1
	3	706	10.0
	4	1523	21.7
Subtotal		3848	54.8
unlikely ADRs	5	438	6.3
	6	399	5.7
	7	389	5.5
Subtotal		1226	17.5
unattributable ADRs	8	808	11.5
Total		7016	100.0

Respondents were significantly more likely to report symptoms potentially caused by the study drug (probable/ possible) than those not likely to be caused by the study drug (unlikely/ unattributable) for each drug ($\chi^2 = 148.632$, df = 8, $P < 0.001$) which is presented in Table 4.18. Patients who reported more symptoms were likely to report more symptoms not known to be caused by the study drugs and which were either classified as unlikely to be an ADR or unattributable (Table 4.19).

Table 4.18 Patient attribution accuracy of symptoms as side effects of drugs

Drug	Frequency of yes criteria* (%)	Frequency of no criteria **(%)	Total (%)
citalopram	303 (84.6%)	55 (15.4%)	358 (100%)
fentanyl patch	68 (72.3%)	26 (27.7%)	94 (100%)
gabapentin	387 (67.3%)	188 (32.7%)	575 (100%)
lamotrigine	70 (59.8%)	47 (40.2%)	117 (100%)
moclobemide	80 (77.7%)	23 (22.3%)	103 (100%)
nefazodone	408 (60.3%)	269 (39.7%)	677 (100%)
topiramate	32 (54.2%)	27 (45.8%)	59 (100%)
tramadol	1567 (67.2%)	766 (32.8%)	2333 (100%)
venlafaxine	2067 (76.6%)	633 (23.4%)	2700 (100%)
Total	4982 (71.0%)	2034 (29.0%)	7016 (100%)

* yes criteria = reported symptoms potentially caused by study drugs (probable/ possible)
** no criteria = reported symptoms not likely to be caused by study drugs (unlikely/ unattributable)

Table 4.19 Number of reported symptoms in relation to number of patients reporting at least one symptom classified as unlikely ADRs and unattributable

Number of reported symptoms	N	No. of patients reporting ≥1 unlikely ADR (%)	No. of patients reporting ≥1 unattributable symptoms (%)
≤ 5	408	79 (19.4%)	107 (26.2%)
6-10	171	78 (45.6%)	119 (69.6%)
11-15	110	79 (71.8%)	94 (85.5%)
>15	148	131 (88.5%)	137 (92.6%)

4.2 Discussion

The overall response rate of the main study (40.1%) was lower than that from the pilot study (44.6%) which may have been due to not sending a reminder to nonrespondents. The reason for this was it was felt this may upset patients who had serious illness and were not willing to participate in this study. There were 87 invalid questionnaires returned, resulting in a final response rate of 36.3%. These invalid questionnaires included those which were returned but not completed (n=10), those returned from patients who were unable to complete the questionnaire either because of their disease state(s) or illiteracy (n=11), those who had deceased (n=21), those who could not remember taking the study drug and those who had not taken the study drug (n=24). A higher response rate (51%) was found in a prospective observational study based on telephone interviews to identify new health problems associated with a NSAID by patient self-reporting (Willison et al., 1995). This study recruited patients by direct contact from individuals who went to the participating pharmacies to fill new or repeat prescriptions for NSAIDs, while the present study recruited patients by mailing a questionnaire. Pharmacist recruitment could therefore be a potential means of increasing response rates.

The majority of the respondents were prescribed tramadol and venlafaxine which represented 41% and 31% of the total respondents, respectively. The remaining seven drugs represented both 27% of questionnaires issued and 27% of respondents. The highest response rate was found in patients prescribed topiramate, while the lowest was in those prescribed fentanyl patch. Considering the different types of study drugs, the average response rates for anticonvulsants (gabapentin, lamotrigine and topiramate) (55.6%) were higher than for antidepressants (citalopram, moclobemide,

nefazodone and venlafaxine) (38.0%) and analgesics (fentanyl patches and tramadol) (31.6%). It is possible that patients prescribed either tramadol or fentanyl patch as a pain killer had serious illness, i.e. cancer, therefore were unable to respond to the questionnaires sent or they had already deceased. This is supported by the finding that nine (43%) and seven (33%) out of a total of 21 invalid questionnaires returned because patients had deceased, were from those prescribed tramadol and fentanyl patch respectively. Additionally, most of the 23 invalid questionnaires returned because patients did not remember taking the study drugs or actually did not take them, 18 (78%) were from patients prescribed tramadol. This may have contributed to lower response rate for tramadol. As was found in the pilot study, patients with depression may have been less willing to participate than those with epilepsy.

Approximately two-thirds of the respondents were female which concords with the pilot study, a patient self-monitoring study by Fisher et al. (1993) and a patient self-reporting study in patients prescribed ophthalmic medications by Barber and Santanello (1995). The greater number of female respondents on antidepressants (70% of all respondents on antidepressants) was probably related to the higher prevalence of depression in females (Lloyd, 1995). The respondents in the main study (mean age = 50.5, majority aged 40-59) seemed to be younger than those in the pilot study (mean age = 54.5, majority aged 60-79) but older than those in the study by Fisher et al. (1993) (mean age = 45.3 for fluoxetine-treated patients). Also, as in the pilot study, no significant differences were found between the sexes in the age distribution. However the number of concomitant drugs being taken was greater in females. About half of the respondents were taking 1-3 concomitant drugs and one quarter were taking 4-6 drugs, the same proportions found in the pilot study. In addition, the analysis again indicated no relationship between increasing age and

number of concomitant drugs. This is in agreement with a study to monitor medication problems in the elderly by Pongwecharak (1998).

A study involving factors influencing the reporting of symptoms by Ciccolunghi and Chaudri (1975) revealed that 63 (97%) out of a total of 65 drug-treated subjects reported at least one symptom through a 38-item checklist questionnaire. However, the present study found a lower proportion (88.6%) of the respondents reported at least one symptom. This is most likely to be related to the small numbers involved in the study by Ciccolunghu and Chaudri, compared to the present study, which consequently had a higher possibility of finding patients who reported no side effects. The fact that the questionnaire designed for the present study was generic, listing potential side effects related to any drug, not only for the study drug and therefore had many more symptoms listed than the 38-item checklist used by Ciccolunghi and Chaudri could also have resulted in a lower number of patients reporting at least one symptom. This may indicate that increasing the number of symptoms listed in the questionnaire appears to diminish over-reporting which could occur through suggestion using specific short checklist questionnaires. Furthermore, a patient self-reporting study to find out new health problems related to NSAIDs using telephone interviews found a much lower percentage of patients (19%) reported at least one new health problem (Willison et al., 1995), compared with the present study. A study by Fisher et al. (1995) also found that only 31.4% and 19.7% of sertraline-treated and fluoxetine-treated patients, respectively, called at least once to report one or more adverse events, while a study to determine patient-perceived side effects to antihypertensive drugs using a closed questionnaire at each clinic visit found that 75.4% of patients reported at least one symptom (Curb et al., 1985). These differences may indicate that using checklist questionnaires as a tool could result in more symptoms reported and probably detects more symptoms related to drugs than

the interview methods (Ciccolunghi and Chaudri, 1975). However, the use of questionnaires may also lead to respondents reporting a large number of symptoms which are unattributable to the study drugs. In the present study, 10.1% and 11.5% of reported symptoms in the pilot and main studies respectively could not be attributed to any known cause. As the drugs involved in the main study were relatively new and subject to 'black triangle' reporting to the CSM, it is possible that some of these symptoms were previously unrecognised ADRs. However the similarity in the frequency with which unattributable symptoms were reported between the main study and the pilot study suggests it is more likely that the type of questionnaire used may have resulted in these high numbers of reports. This is supported by the finding that the number of unattributable symptoms increased with the total number of symptoms reported. Consequently, patients who reported more symptoms seemed to be worse discriminators since they reported more unattributable symptoms.

Patients prescribed anticonvulsants appeared to report fewer different symptoms than those prescribed antidepressants. This may indicate that antidepressants caused more different side effects than anticonvulsants. However, it is much more likely that this was due to the difference in sample size, since patients taking anticonvulsants (n=99) were much lower in number than patients taking antidepressants (n=386). Patients prescribed fentanyl patches reported the highest median of different symptoms, although they were fewest in number. This is most likely due to biases from some patients within such a small group prescribed this drug who reported high numbers of symptoms. The lowest number of different symptoms were reported by patients taking topiramate (41) and lamotrigine (46), while the highest ranges were reported by patients taking tramadol (97) and venlafaxine (92). This again may indicate that increasing the number of respondents was likely to increase the number of different symptoms reported since those taking tramadol and venlafaxine accounted

for 74.3% of the total respondents. Combining the results from both the pilot and main studies suggests that the number of different symptoms reported is low with numbers of respondents below 25, but that large increases in the number of respondents above 25 does not result in a large increase in the number of different symptoms reported. This supports the use of such questionnaires as a tool for reporting of potential adverse effects, since it suggests that the symptoms reported do conform to a pattern, rather than being randomly distributed.

The results suggest that patients receiving the new CNS drugs studied experienced a wide range of side effects. While it may be that in fact patients taking these drugs had truly experienced those side effects, it may be that patients took a broad view of the term 'side effect' used in the questionnaire. For example, some of the symptoms reported appeared to be unrelated to the information obtained on either the disease states or its treatment. These could be attributed to other medication being taken or other conditions not listed on the questionnaires by respondents. Despite the fact that the questionnaire included various statements in an attempt to focus patients' thinking (namely: 'please be assured this does not mean your medicine can cause all of the side effects listed here', 'Only indicate the problems which were not present before you started taking *study drug name*' and 'Have you had any of the following symptoms which you think may be due to side effects from this medicine'), the respondents may nonetheless have had the impression that they were expected to experience many of the effects listed. They may also have experienced an increase in side effects due to suggestion from the symptoms listed in the questionnaires, particularly mild signs and symptoms. Indeed, many of the unattributable symptoms reported could have been due to suggestion as was mentioned by Borghi et al. (1984). However, evidence from other contexts suggests that informing patients of potential side effects does not lead to an increased incidence of those side effects (Rickels and Downing, 1970; Lamb,

1994; Howland et al., 1990). The questionnaire design was an attempt to reduce bias caused by suggestion. It listed many potential ADRs applicable to any drug, not just the study drugs as previously mentioned in Chapter 2. Also, as these problems were anticipated, the classification of causal relationship was established to provide an interpretation of how accurately patients attributed the symptoms to the study drugs.

As found in the pilot study, the main study found no positive relationship between increasing age and number of reported symptoms for all study drugs. In fact, some studies have found an association between increasing age and incidence of ADRs experienced (Walker and Wynne, 1994; O' Donnell, 1994; Cuningham et al., 1997) although others have not found this association (Nelson and Talbert, 1996; Moore et al., 1998). The present study revealed no relationship between increasing age and the number of concomitant drugs being taken, therefore if polypharmacy is related to the number of experienced ADRs, this may account for the lack of relationship between increase in age and number of reported symptoms in this study. Unlike the pilot study, the main study found no difference in number of symptoms reported between males and females, despite females having been reported to suffer more ADRs than males (O' Donnell, 1994; Cunningham et al., 1997).

The study also showed no relationship between increasing number of concomitant drugs and number of reported symptoms. Studies by Hallas et al. (1991), Pongwecharak (1998) and Fisher et al. (1993) found no association between the number of prescribed drugs and the incidence of medication-related problems which included ADRs. Conversely, other studies have reported polypharmacy to be a predictor of ADRs among several groups of hospitalised patients including the elderly, critical care patients, patients undergoing complicated surgical procedures and patients admitted to general medical wards (May, 1997; Moore et al., 1998;

Cunningham et al., 1997; Classen et al., 1997; Nelson and Talbert, 1996; Lee, 1993). However the present study suggests that increasing the number of concomitant drugs does not affect the incidence of ADRs. Possible reasons for this may be that any association between concomitant drugs taken and number of ADRs experienced may have been masked by patients not reporting all ADRs which they experienced and not having the opportunity for discussion with a researcher. This study was undertaken in out-patients, while most of the studies in which a relationship was found were carried out in in-patient populations. Thus, patients who participated in this study were less seriously ill and more likely not to report any ADR which had disappeared before they completed the questionnaires. Furthermore, patients may have become accustomed to those ADRs whose onset was several months ago and consequently not bothered to report them. These latter points may also explain why in the present study patients who had been taking the study drugs for longer did not report significantly more symptoms than those with a shorter duration of therapy. This finding is different from the work of Fisher et al. (1993, 1995) which took duration of exposure to the study drugs into account statistically as a confounding factor affecting adverse clinical events reported. However, another reason for this difference may be that the main study involved patients taking only newly marketed drugs which have less widespread use and total exposure time than older drugs. This point resulted in the majority of respondents having a drug exposure time in this study of less than one and a half years (61.6%), so there were too few patients who had a longer exposure time to the study drugs to demonstrate whether or not an increase in duration of therapy could increase the number of ADRs experienced and reported. In addition, there was no evidence from this study of increasing frequency of drug taking leading to an increase in the number of symptoms reported. As expected, the vast majority (87%) of patients had taken one of the nine study drugs in the recommended dosage regimen with the frequency of one or two times a day. Of those patients who had taken study drugs

more frequently, the doses were still in the normal ranges recommended. It is therefore unlikely that more ADRs would be experienced and reported. The data from the present study also suggests that patients who were taking other drugs with the same indication as the study drugs had no significant increase in the number of reported symptoms, compared with the rest. However, patients taking any other CNS drugs reported more symptoms than those not taking other CNS drugs. This could be because taking other CNS drugs would increase in number of different side effects experienced and lead to an increase in number of symptoms reported, while the same side effects would be caused by drugs of the same class.

Severity of the most bothersome symptoms reported was graded into five levels as minimally, mildly, moderately, severely and very severely by 70% of respondents. The result showed that patients tended to rate the severity of their most bothersome symptoms more than minimally or mildly with the majority selecting moderately and severely (49.1%). This finding is in line with the pilot study and the studies by Fisher et al. (1993), Fisher (1995) and Buckingham et al. (1997). As in the pilot study, 15% of total respondents rated the severity as 'does not apply'. The severity was regrouped into three levels as mild, moderate and severe for statistical analysis. There were no statistical differences among these three degrees of severity with regard to duration of therapy, frequency of drug taken, whether patients were taking other CNS drugs or other drugs for the same indication as the study drugs. Conversely, a greater proportion of patients who rated the most bothersome symptoms as severe were found to inform their doctors about these symptoms than those who rated the severity as mild. This suggests that patients with more severe symptoms were concerned about these symptoms, which led them to report them to their doctors. In the pilot study there was a trend towards a similar relationship between the severity of symptoms and whether patients reported the symptoms to their doctors. It is possible

that patients taking the newer drugs in the main study may have been more concerned about any effect they perceived to be related to these drugs than those who were taking the older drugs in the pilot study. Nevertheless, Fisher (1995) found many more patients taking an older drug (trazodone) reporting well known ADRs, when compared with a newer drug (fluoxetine). The relationship between severity of symptoms reported and number of drugs being taken concomitantly was not statistically significant, although there were higher percentages of patients who reported the most bothersome symptoms as severe who were taking four or more other drugs, compared with those who reported the symptoms as moderate and mild. Mannesse et al. (1997) also found the use of three of more drugs was a significant factor in patients with severe adverse reactions. The results showed a significant relationship between the severity of symptoms reported and number of reported symptoms. This suggests that patients were much more likely to report symptoms in the questionnaires that were particularly subjectively severe and bothersome to them which is similar to the findings of the pilot study and studies by Fisher et al. (1995) and Fisher (1995).

With regard to the accuracy of patients' attribution of symptoms to study drugs, the majority of symptoms were classified as possibly (54.3%) or probably (16.2%) caused by the study drugs. Therefore, a large number of symptoms reported could also be attributed to concomitant drugs or patients' disease states (possible ADRs), while only 16.2% of symptoms reported could be attributed to only the study drugs (probable ADR). One of the limitations of any patient self-reporting is that data are mainly obtained from patient perceptions and recollections, although in this study further data were also obtained from the medical records in some cases. Nonetheless, it is difficult for patients and even health professionals to judge which symptoms were caused by drugs with certainty. This view is broadly in agreement with other studies in that one of the main reasons for doctors not reporting an ADR was uncertainty about whether the

reaction was caused by the suspected drug (Scott et al., 1987; Bateman et al., 1992; Inman and Weber, 1986; Randhawa et al., 1987). Although there have been many attempts to reduce the uncertainty by creating various criteria to assess the causality of ADRs (Karch and Lasagna, 1977; Kramer et al., 1979; Naranjo et al., 1981; Venulet, 1986a), such methods are still unable to conclude that the suspected drugs truly caused the reactions or eliminate the uncertainty. They only categorise ADRs into levels of probability. The need to develop a new classification system, based on different criteria, arose because of the lack of additional data available to enable any of these standard criteria to be used. It must also be emphasised that in most cases, information on concurrent drugs and disease states was only obtained from patients, and therefore may be incomplete or unreliable. However, using this classification in this large cohort of patients, as with the pilot study, it was found that patients appeared to be capable of correctly identifying possible ADRs caused by the study drugs, accounting for 71.0% of reported symptoms. This again is in line with the estimate of Fisher et al. (1994).

The results showed a relationship between increasing number of reported symptoms and the proportion of patients reporting symptoms not known to be caused by the study drugs. This finding is in agreement with the pilot study and again suggests that patients who reported more symptoms seemed to be representative of worse discriminators since they tended to report more symptoms classed as either unlikely ADRs or unattributable. This could also have led to bias due to over-reporting by those patients.

Chapter 5

Results and Discussion:

Main study: Tramadol

5.1 Results

5.1.1 Response rate and demographic data

There was a total of 1048 postal questionnaires sent to patients prescribed tramadol. Of these, 344 patients valid responses were obtained, representing a response rate of 32.8%. Of the total respondents, 115 (33.4%) were male and 227 (66.0%) were female, two (0.6%) did not specify. The mean ± SD age of the respondents was 57.4 ± 17.0 of which the majority were in age groups were 60-79 (38.9%) and 40-59 (33.4%). Table 5.1 lists number of respondents in different age groups.

Table 5.1 Number of respondents prescribed tramadol according to age groups

Age group	Number of respondents	%
< 20	1	0.3
20-39	58	16.9
40-59	115	33.4
60-79	134	38.9
≥ 80	31	9.0
not specified	5	1.5
Total	344	100

5.1.2 Drug therapy

Table 5.2 shows concomitant drugs being taken by number of respondents. The majority of the respondents (81%) were taking between one and six concomitant drugs. The mean ± SD number of concomitant drugs was 3.7 ± 2.3 (range 0-16). There was no strong relationship between increasing age and number of concomitant drugs (Spearman r = 0.19743, P < 0.001). The average duration of taking tramadol was 324.8 days (SD = ± 348.1) with approximately one-third of the respondents (31.7%) taking it for between 1-180 days. Of the total respondents, 32.6%, 25.9% and 20.6% had taken tramadol two, three and four times daily, respectively. The most frequent indication for taking tramadol was back pain (25.3%) which was followed by other bone or muscle pains (17.7%), unspecified pain (17.2%) and osteoarthritis (15.4%) as shown in Table 5.3. Two hundred and twenty three respondents (64.8%) reported that they also had other medical conditions. Although 137 respondents (39.8%) reported that they had been in hospital after starting tramadol, none of them indicated that the admissions had been caused by tramadol. Twenty seven percent of the 126 respondents who had stopped taking tramadol did so because they felt that they did not need the drug any longer and a further 20% felt the drug was not helping them (Table 5.4). Thirty-eight respondents (11.0% of the total 344 respondents) claimed to have stopped taking it because either they or their doctor identified a problem with it.

Table 5.2 Number of respondents prescribed tramadol according to number of concomitant drugs

Number of concomitant drugs	Number of respondents	%
0	12	3.5
1-3	149	43.3
4-6	129	37.5
7-9	29	8.4
≥10	5	1.5
Not specified	20	5.8
Total	344	100

Table 5.3 Number of respondents prescribed tramadol according to indication for use

Indication	Number of respondents	%
Osteoarthritis	53	15.4
Rheumatoid arthritis	8	2.3
Spondylosis	3	0.9
Degenerative bones or joints	16	4.7
Other bone or muscle pains	61	17.7
Trigeminal neuralgia	1	0.3
Back pain	87	25.3
Cancer pain	3	0.9
Colic pain	24	7.0
Headache	10	2.9
Unspecified pain	59	17.2
No indication given	19	5.5

Table 5.4 Reasons for stopping tramadol cited by 126 respondents

Reason	Number of respondents	%
I felt I didn't need it any longer.	34	27.0
The doctor said I didn't need it any longer.	17	13.5
The doctor told me to stop as I was having problems with it.	19	15.1
I decided to stop as I was having problem with it.	19	15.1
I felt it wasn't helping me	25	19.8
Others	10	7.9
Not specified	2	1.6
Total	126	100

5.1.3 Symptoms reported

Of the total 344 respondents prescribed tramadol, 289 (84.0%) reported at least one symptom, while 55 (16.0%) reported no side effects experienced. There were 92 different symptoms and 2333 total symptoms reported (median = 4.5, range = 0-51). No significant relationship between the number of reported symptoms and age (Spearman r = 0.027), number of concomitant drugs (Spearman r = 0.071) or duration of therapy (Spearman r = 0.209) was found in the respondents prescribed tramadol. Two hundred and three (59.0%) and 120 (34.9%) of the 344 respondents were taking other analgesics and other CNS drugs, respectively. Patients who were taking other analgesics reported similar numbers of symptoms to those who were not taking other analgesics in addition to tramadol (χ^2 = 0.766, df = 3, P-value = 0.858). On the other

hand, patients taking any other CNS drugs together with tramadol were likely to report more symptoms than those not taking other CNS drugs (χ^2 = 9.567, df = 3, P = 0.023) as demonstrated in Table 5.5.

Table 5.5 Presence of other CNS drugs concomitant with tramadol in relation to number of reported symptoms

Presence of other CNS drugs	Number of patients (%)				
	Number of reported symptoms				Total* (%)
	≤ 5	6-10	11-15	>15	
No	115 (59.0%)	36 (18.5%)	29 (14.9%)	15 (7.7%)	195 (100%)
Yes	64 (53.3%)	20 (16.7%)	13 (10.8%)	23 (19.2%)	120 (100%)

* Total number of valid cases = 315

Of the total 344 respondents, 93 (27.0%) and 48 (13.9%) perceived the severity of their most bothersome symptoms as moderate and severe, respectively. Approximately one-fifth of the respondents claimed they had informed their doctors about all symptoms reported in the questionnaires and a similar proportion had told their doctors about some of the symptoms they reported (Table 5.6). Patients who perceived the most bothersome symptoms as severe were significantly more likely to inform their doctors about symptoms reported in the questionnaires, compared with those who perceived the symptoms as mild (χ^2 = 11.052, df = 2, P = 0.004) which is shown in Figure 5.1. There was also a significant association between the number of reported symptoms and severity rating of the most bothersome symptoms (χ^2 = 14.585, df = 6, P = 0.024) as presented in Figure 5.2.

Table 5.6 Number of respondents prescribed tramadol according to severity of most bothersome symptoms and whether they informed their doctors.

	No. of respondents	%
Severity		
minimally	15	4.4
mildly	25	7.3
moderately	93	27.0
severely	48	13.9
very severely	24	7.0
does not apply	71	20.6
not specified	68	19.8
Inform doctors		
all of symptoms	77	22.4
some of symptoms	70	20.3
none of symptoms	72	20.9
not sure	23	6.7
does not apply	57	16.6
not specified	45	13.1

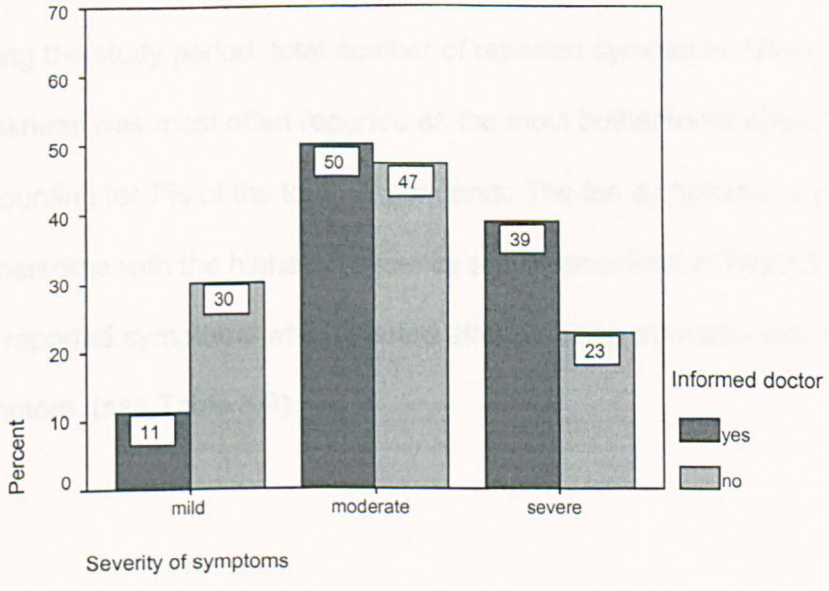

Figure 5.1 Severity of most bothersome symptoms reported by patients prescribed tramadol in relation to whether patients reported symptoms to their doctor

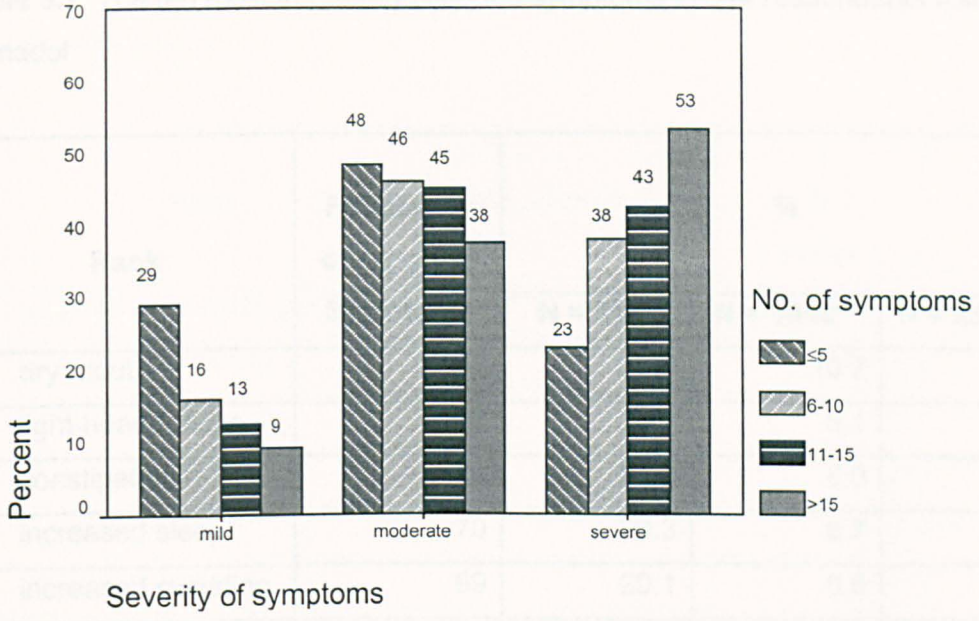

Figure 5.2 Severity of most bothersome symptoms in relation to number of symptoms reported by patients prescribed tramadol

Dry mouth, light-headedness and constipation were the three most commonly reported symptoms by patients prescribed tramadol. Table 5.7 shows the ten most commonly reported symptoms of tramadol expressed as percentages using different denominators, i.e. number of respondents, number of patients prescribed tramadol during the study period, total number of reported symptoms. Unusual tiredness or weakness was most often reported as the most bothersome effect of tramadol, accounting for 7% of the total respondents. The ten symptoms reported as most bothersome with the highest frequency are summarised in Table 5.8. Only one of the ten reported symptoms which started after stopping tramadol was a known withdrawal symptom. (see Table 5.9)

Table 5.7 The ten most frequently reported symptoms in 344 respondents taking tramadol

Rank	Frequency of reported Symptoms	%		
		N = 344*	N = 1048**	N = 2333***
1. dry mouth	112	32.6	10.7	4.8
2. light-headedness	85	24.7	8.1	3.6
3. constipation	84	24.4	8.0	3.6
4. increased sleep	70	20.3	6.7	3.0
5 increased sweating	69	20.1	6.6	2.9
6. flushing	67	19.5	6.4	2.9
7. nausea/ vomiting	66	19.2	6.3	2.8
8. unusual tiredness/ weakness	65	18.9	6.2	2.8
9. itching of skin	65	18.9	6.2	2.8
10. dizziness/ vertigo	56	16.3	5.3	2.4

* number of total respondents

** number of total questionnaires sent

*** total number of reported symptoms

Table 5.8 The ten most frequent symptoms reported as most bothersome by patients prescribed tramadol

Rank	No. of patients*	% (n=344)
1. unusual tiredness/ weakness	24	7.0
2. increased sweating	23	6.7
3 reduction in sleeping	14	4.1
4. change in mood	13	3.8
5. constipation	11	3.2
6 excessive thirst	11	3.2
7. itching of skin	10	2.9
8. bone or joint pain	10	2.9
9. nausea/ vomiting	10	2.9
10. light-headedness	10	2.9

* total frequency of most bothersome symptoms = 314

Table 5.9 Frequency of reported symptoms which started after stopping tramadol

Symptoms	Frequency of reported symptoms* (%) (n = 344)
1. muscle weakness	1 (0.3%)
2. unsteadiness on feet	1 (0.3%)
3. itchy or irritated eyes	1 (0.3%)
4. tinnitus	1 (0.3%)
5. dry mouth	1 (0.3%)
6. decreased in sexual desire	1 (0.3%)
7. decreased in sexual ability	1 (0.3%)
8. increased sleep	1 (0.3%)
9. reduction in sleeping @	1 (0.3%)
10. not specified	1 (0.3%)
Total	10 (3.0%)

* number of patients reporting these symptoms = 10

@ known withdrawal symptoms

5.1.4 Comparison between symptoms reported in the questionnaire and in medical notes

Data was obtained from the medical records of 50 of the respondents prescribed tramadol. Of the total 315 symptoms reported by the 50 patients in the questionnaires, only 66 (20.9%) were recorded by GPs in the medical notes. Of these, 59 (89.4%) were recorded in the medical notes as symptoms, three (4.5%) were recorded as side effects of tramadol and four (6.1%) were recorded as side effects of other drugs taken. There were seven reports describing a total of 17 symptoms related to tramadol from the Grampian region sent to the CSM over the same period (1 July 1996 – 31 August 1997). Ten (20%) and six (12%) of the total 50 respondents reported complete

information in the questionnaire about concomitant drugs and disease states, respectively, compared with the records in their medical notes. The ten most commonly reported symptoms in the questionnaire and the frequency with which these were recorded in the medical notes are compared in Table 5.10.

Table 5.10 Comparison of the ten most frequently symptoms of tramadol reported by patients in questionnaires with those recorded by doctors in medical notes

Rank	Frequency of reported symptoms (n= 50)		% availability in medical notes
	Questionnaires	Medical notes	
1. dry mouth	9	0	0
2. light-headedness	10	0	0
3. constipation	10	2	20
4. increased sleep	11	1	9
5 increased sweating	9	1	11
6. flushing	10	3	30
7. nausea/ vomiting	12	5	42
8. unusual tiredness/ weakness	16	4	25
9. itching of skin	7	1	14
10. dizziness/ vertigo	7	1	14

5.1.5 Comparison between symptoms reported in the present study with CSM data

Of the ten most common symptoms reported by patients prescribed tramadol in the present study, five were also one of the ten most commonly reported symptoms from CSM data. These were increased sleep, increased sweating, nausea/ vomiting, itching of skin and dizziness/ vertigo. Table 5.11 compares the frequency of the ten most frequently reported symptoms in the present study with CSM data together with a frequency ranking for CSM reports. The study data was compared with the CSM data using total frequency of reported symptoms as a denominator. Considering each individual symptom, nine of the ten most commonly reported symptoms in the present study were reported in significantly different proportions from those in CSM data. Only increased sweating was reported with similar frequency ($Z = -0.97$, 95% CI = -1.49 – 0.51%, $P = 0.333$). Headache, rashes, hallucinations, convulsions, confusion and nausea/ vomiting and dizziness/ vertigo, which were the top ten symptoms reported from CSM data, were all reported with higher frequency to the CSM by prescribers than by patients in the current study (Table 5.12). Many patients reported dry mouth, light-headedness, constipation, flushing and unusual tiredness/ weakness. These symptoms were infrequently reported to the CSM.

Table 5.11 Comparison of the ten most frequently reported symptoms to tramadol in the present study with CSM data

Rank	Frequency of reported symptoms (%)		P-value***	CSM ranking No.
	Own study*	CSM data**		
1. dry mouth	112 (4.8%)	24 (1.0%)	< 0.001	20
2. light-headedness	85 (3.6%)	19 (0.8%)	< 0.001	25
3. constipation	84 (3.6%)	19 (0.8%)	< 0.001	25
4. increased sleep@	70 (3.0%)	48 (2.0%)	0.027	10
5 increased sweating@	69 (2.9%)	83 (3.5%)	0.333	6
6. flushing	67 (2.9%)	18 (0.7%)	< 0.001	27
7. nausea/ vomiting@	66 (2.8%)	366 (15.2%)	< 0.001	1
8. unusual tiredness/ weakness	65 (2.8%)	42 (1.7%)	0.016	13
9. itching of skin@	65 (2.8%)	96 (4.0%)	0.021	5
10. dizziness/ vertigo@	56 (2.4%)	176 (7.3%)	< 0.001	2

* denominator = total frequency of reported symptoms = 2333 (n = 344)

** denominator = total frequency of reported symptoms = 2404 (n=1185)

*** Z-test

@ one of the ten most frequently reported symptoms from CSM data

Table 5.12 Comparison of the ten most frequently reported symptoms to tramadol in CSM data with the present study

Rank	Frequency of reported symptoms (%)		P-value***
	CSM data*	Own study**	
1. nausea/ vomiting@	366 (15.2%)	66 (2.8%)	< 0.001
2. dizziness/ vertigo@	176 (7.3%)	56 (2.4%)	< 0.001
3. headache	123 (5.1%)	40 (1.7%)	< 0.001
4. rashes	119 (4.9%)	20 (0.9%)	< 0.001
5. pruritus@	96 (4.1%)	65 (2.8%)	0.021
6. increased sweating@	83 (3.5%)	69 (3.0%)	0.333
7. hallucinations	80 (3.3%)	8 (0.3%)	< 0.001
8. convulsions	54 (2.2%)	4 (0.2%)	< 0.001
9. confusion	53 (2.2%)	13 (0.6%)	< 0.001
10. increased sleep@	48 (2.0%)	70 (3.0%)	0.027

* denominator = total frequency of reported symptoms = 2404 (n=344)

** denominator = total frequency of reported symptoms = 2333 (n =1185)

*** Z-test

@ one of the ten most frequently reported symptoms of the present study

5.1.6 Comparison between symptoms reported in the present study and PEM data

The number of patient-months of treatment was calculated, where data was available, to provide a comparative denominator to a PEM study. Higher proportions were found for eight of the ten most commonly reported symptoms in the present study, while only nausea/ vomiting had lower proportions, compared with PEM data (Z = - 4.68, 95% CI = -1.81 - -0.74%, P = <0.001). Only dizziness/ vertigo was found to have no statistically significant difference in the proportions of reports between the present study and PEM study (Z= 0.23, 95% CI = -0.38 –0.49%, P = 0.814). However, it was revealed that three of the ten most frequently reported symptoms in the present study were also found to be among the ten most frequently reported events from PEM data. These were nausea/ vomiting, dizziness and fatigue or weakness. In addition, six of the ten most frequently reported symptoms in this study were among the 20 most frequently reported events of PEM data (Table 5.13).

Table 5.13 Comparison of the ten most frequently reported symptoms to tramadol in the present study with PEM data

Rank	Frequency of reported Symptoms (%)		P-value***
	Own study*	PEM data**	
1. dry mouth	89 (2.88%)	27 (0.12%)	< 0.001
2. light-headedness	74 (2.40%)	42 (0.19%)	< 0.001
3. constipation@	63 (2.04%)	133 (0.59%)	< 0.001
4. increased sleep@	62 (2.01%)	165 (0.73%)	< 0.001
5 increased sweating@	54 (1.75%)	47 (0.21%)	< 0.001
6. flushing	56 (1.81%)	13 (0.06%)	< 0.001
7. nausea/ vomiting@	59 (1.91%)	719 (3.19%)	< 0.001
8. unusual tiredness/ weakness@	56 (1.81%)	147 (0.65%)	< 0.001
9. itching of skin	50 (1.62%)	52 (0.23%)	< 0.001
10. dizziness/ vertigo@	42 (1.36%)	295 (1.31%)	0.814

* denominator = total number of patient-months of treatment = 3086 (number of valid patients = 285)

** denominator = total number of patient-months of treatment = 22539

*** Z-test

@ one of the 20 most frequently reported events from PEM data

5.1.7 Comparison between symptoms reported in the main study and the pilot study

Co-proxamol was the analgesic in the pilot study to which tramadol was compared. Six of the ten most frequently reported symptoms to tramadol were also among the top ten reported with co-proxamol. The frequencies of many of the symptoms reported with both drugs were similar (Table 5.14). However light-headedness, increased sleep and nausea/ vomiting were reported significantly more frequently with tramadol.

Table 5.14 Comparison of the ten most frequently reported symptoms of tramadol with co-proxamol

Rank	Frequency of reported symptoms (%)		P-value**
	Tramadol* (n= 344)	Co-proxamol* (n= 45)	
1. dry mouth@	112 (32.6%)	10 (22.2%)	0.123
2. light-headedness	85 (24.7%)	6 (13.3%)	0.041
3. constipation@	84 (24.4%)	11 (24.4%)	0.997
4. increased sleep	70 (20.3%)	4 (8.9%)	0.016
5 increased sweating	69 (20.1%)	5 (11.1%)	0.083
6. flushing@	67 (19.5%)	10 (22.2%)	0.675
7. nausea/ vomiting	66 (19.2%)	1 (2.2%)	< 0.001
8. unusual tiredness/ weakness@	65 (18.9%)	7 (15.6%)	0.565
9. itching of skin@	65 (18.9%)	9 (20.0%)	0.861
10. dizziness/ vertigo@	56 (16.3%)	8 (17.8%)	0.804

* denominator = number of total respondents

** Z-test

@ one of the top ten most frequently reported symptoms of co-proxamol

5.1.8 Patient attribution of symptoms to drugs

Of the total number of perceived symptoms reported, 1246 (53.4%) were classified by the researcher as being possibly caused by the study drugs, with a further 321 (13.8%) classed as probably caused by study drugs. Four hundred and fifty six symptoms (19.5%) were classed as unlikely to be an ADR and 310 were unattributable (13.3%). Table 5.15 lists the result of the classification for causal relationship of the perceived symptoms according to the eight criteria. The highest frequency was of those symptoms which could be caused by the study drug and concomitant drugs (criteria 2). Also, there were a large number which could have been caused by concurrent disease states in addition to drugs being taken (criteria 4). A greater proportion of respondents (67.2%) reported symptoms potentially caused by tramadol (probable/ possible) than those (32.8%) not likely to be caused by tramadol (unlikely/ unattributable).

Table 5.15 Classification of symptoms reported by patients prescribed tramadol into eight criteria for assessment of causal relationship

Causal relationship	Criteria	Total frequency of reported symptoms	
		No.	%
probable ADRs	1	321	13.8
possible ADRs	2	790	33.9
	3	79	3.4
	4	377	16.2
Subtotal		1246	53.4
unlikely ADRs	5	222	9.5
	6	105	4.5
	7	129	5.5
Subtotal		456	19.5
Unattributable ADRs	8	310	13.3
Total		2333	100

5.1.9 Comparison between expert and researcher opinion on the classification for causal relationship

Of a total 315 symptoms reported by 50 patients whose medical notes were accessed and evaluated, 219 symptoms (69.5%) were jointly agreed and 96 symptoms (30.5%) were disagreed between the expert and the researcher using the four categories of causal relationship. Considering each criteria of the causal relationship, 0 (0%), 169 (53.7%), 40 (12.7%) and 10 (3.2%) of the symptoms reported were mutually agreed with the classifications as probable, possible, unlikely and unattributable, respectively (Table 5.16). Kappa value for agreement between the expert and the researcher was 0.43 indicating moderate agreement (Altman, 1992).

Table 5.16 Comparison of expert and researcher classifications of symptoms reported from tramadol into four criteria according to causal relationship

Researcher Classifications	**Number of reported symptoms by expert classifications (%)**				**Total**
	Probable	Possible	Unlikely	Unattributable	
Probable	0 (0%)	20 (6.3%)	5 (1.6%)	2 (0.6%)	27 (8.6%)
Possible	0 (0%)	169 (53.7%)	25 (7.9%)	5 (1.6%)	199 (63.2%)
Unlikely	0 (0%)	9 (2.9%)	40 (12.7%)	7 (2.2%)	56 (17.8%)
Unattributable	0 (0%)	7 (2.2%)	16 (5.1%)	10 (3.2%)	33 (10.5%)
Total	0 (0%)	205 (65.1%)	86 (27.3%)	24 (7.6%)	315 (100%)

5.2 Discussion

The response rate for patients prescribed tramadol (32.8%) was lower than that for the remaining drugs in the main study (39.2%), although the number of respondents was largest (n= 344). The majority of respondents prescribed tramadol were elderly (60-79). This is most likely due to the majority of respondents being prescribed tramadol for musculoskeletal problems (n=228, 66.3%) which presumably occur more frequently in the older age group. Again, there was no evidence of a relationship between increasing age and number of concomitant drugs in respondents taking tramadol which was in accordance with the pilot study. Approximately one-third of the respondents had taken tramadol for less than six months, however the mean duration of therapy was 325 days. This suggests that the majority of respondents suffered from chronic pain which related to their disease states, particularly musculoskeletal problems which are frequently chronic in nature.

The number of respondents taking tramadol for cancer pain was low (n=3). This may not necessarily suggest that tramadol was not frequently prescribed for cancer pain. It may indicate that cancer patients were less able to respond to the questionnaires sent due to severity of illness, compared with those suffering from musculoskeletal diseases. The response rate to fentanyl patches, which are most frequently prescribed for cancer pain was also low. Not surprisingly, tramadol was also prescribed in only a small number of respondents for minor pains, such as headache, as its indication is for moderate and severe pain.

Interestingly, the data show that 51 (14.8%) of the respondents had stopped taking tramadol since their medical condition had improved. This suggests that tramadol was

also being used for acute conditions. Thirty-eight respondents (11.0%) perceived that problems had caused them to discontinue tramadol, with or without their doctor's recommendation. The percentage of the respondents who discontinued tramadol was lower than that of a more recent study to examine the effect of three titration schedules on the tolerability of tramadol by Ruoff (1999) which found 15.2-30.8% of patients discontinued tramadol during day 1- day 10 of the titration schedule because of adverse events. This difference is probably because patients in the present study had already passed the titration period which is normally at the beginning of therapy. Twenty five (7.3%) of the respondents who had discontinued the drug had done so because they felt tramadol was not helping them. This suggests that although tramadol is used for moderate or severe pain, it may not be effective enough for relieving pain in some patients.

Eighty-four percent of the respondents taking tramadol reported at least one symptom which was slightly lower than for the rest of the main study (92.3%). However, this result is slightly higher than the 77.8% found by Crighton et al. (1997) in a prospective double-blinded study involving 18 women who received tramadol during laparoscopic sterilisation. The respondents reported a wide range of symptoms (0 – 51) and a high number of different symptoms (95), although the median number of symptoms reported was only 4.5. Some patients may have over-reported symptoms which they suffered regardless of whether the symptoms were caused by tramadol or not, leading to bias. Within this group of respondents there was no positive relationship between increasing age, number of concomitant drugs or duration of therapy with number of symptoms reported.

The severity of the most bothersome symptoms reported was rated into one of five levels as minimally, mildly, moderately, severely and very severely by 60% of the

respondents taking tramadol. Fewer of this group of respondents completed this rating than those taking other drugs (77.1%) while a higher percentage ticked 'does not apply' and 'unspecified'. This is clearly related to the finding that more respondents prescribed tramadol reported they had experienced no side effects than for the remaining drugs (16% vs 7.7%).

Interestingly, only half of the respondents (147/289) who reported symptoms which they thought to be side effects from tramadol had informed their doctors about these. It is likely that the symptoms which they did not inform their doctor were minor side effects and did not bother them. This may also lead doctors to under-detect and under-report ADRs occurring in out-patient populations. This is particularly important for symptoms relating to black triangle drugs which require the reporting of any type of ADR, even minor or known side effects.

As the range of reported symptoms was large, this discussion will concentrate on those which occurred most frequently. Six of the symptoms cited as being most bothersome by the respondents taking tramadol were also among the top ten most frequently reported. These were light-headedness, constipation, increased sweating, nausea/ vomiting, unusual tiredness/ weakness and itching of skin. All of the ten most frequently reported symptoms and nine of the ten most bothersome symptoms reported, except bone or joint pain reported by ten respondents, are known side effects of tramadol. This suggests that the respondents seemed to report mainly symptoms potentially caused by tramadol. However, bone or joint pain which was most likely attributable to patients' disease states was also cited as one of the ten most bothersome symptoms. This suggests that a few patients also appeared to report the symptoms which bothered them a lot even though those symptoms did not relate to the study drug. The large number of respondents reporting potential ADRs however

meant that bone or joint pain was not one of the top ten most frequent symptoms reported.

By taking into account only the number of respondents (n=344) as the denominator, these percentages of symptoms reported could form an estimate of the highest likely incidence of individual side effects, particularly as patients experiencing side effects may be more likely to respond. The lowest likely incidence could be estimated by using the total number of questionnaires sent to patients prescribed tramadol including nonrespondents (n=1048) as the denominator and assuming that nonrespondents did not experience any side effects. Thus, an incidence estimate of dry mouth could range from 10.7% to 32.6%, light-headedness from 8.1% to 24.7% and constipation from 8.0% to 24.4%. These interval estimates could therefore diminish the bias from representative patients who may have had ADRs but did not respond to the questionnaire or those who may have ignored side effects that they were familiar with. However, the method used in this study, involving questionnaire distribution at a single point in time, meant that any patients who had stopped tramadol or were switched to some other drug did not receive the questionnaire. Therefore, while it is a sample of all patients prescribed the drug at a given time, the sample may comprise mainly the 'survivor' patients as described in studies by Fisher et al. (1993, 1995) and Fisher (1995). It is important to note however that since the questionnaire was distributed six months after the prescription was dispensed, 11% of respondents had stopped taking the drug. Therefore the method should have resulted in the inclusion of a more representative sample of those who tolerated tramadol than those who did not.

Ten (2.9%) out of a total 344 respondents reported symptoms which started after stopping tramadol, however only one of these was a known withdrawal symptom of tramadol, reduction in sleep. This confirms a finding reviewed by Budd (1994) from

clinical studies, PMS studies and clinical experience over 15 years that the development of dependence during long term therapy use was uncommon, therefore it was not surprising that few withdrawal symptoms were associated with tramadol in the present study. The other nine symptoms reported such as muscle weakness, unsteadiness on feet, itchy or irritated eyes, tinnitus and dry mouth, may have been related to patients' disease states or concomitant drugs which patients were still taking after discontinuing tramadol.

When compared with symptoms reported by patients taking tramadol in the questionnaires, it was found that the frequency with which symptoms reported by patients recorded in the medical notes was low. Only 20.9% of the 315 symptoms reported by 50 respondents were recorded by GPs in the medical notes which is comparable to the 22% in the pilot study. Of these, only 4.5% were recorded as side effects from tramadol, the rest were recorded as symptoms (89.4%) and side effects from other drugs taken (6.1%). Of the 50 patients whose case notes were studied, 26 (52%) said they had informed their doctors about the symptoms reported. Of these, 18 (69%) had at least one symptom recorded in the case notes. This may suggest that the reporting by patients seems to be reliable. Alternatively, although doctors tended to record symptoms reported to them, only a limited number of those symptoms were recorded in the case notes for each individual patient. This may contribute to the finding that only 21% of total symptoms reported were recorded in case notes. As well as doctors not recording all the symptoms, almost half the patients claimed not to have reported any of the symptoms they identified by questionnaire to their doctors. The symptoms which were most frequently reported in the medical notes were nausea/ vomiting (42%), flushing (30%), unusual tiredness/ weakness (25%) and constipation (20%). Three of these symptoms were among those identified by patients as most bothersome, which may have led them to report the symptoms to their doctors.

Data obtained from the CSM showed that only seven yellow cards including 17 adverse effects to tramadol originated from the Grampian region during the period that patients were asked to report their experiences of ADRs in the questionnaire (i.e. the 12 months prior to completing the questionnaires). These included reports both sent directly to CSM as well as indirectly via the pharmaceutical industry or from the scientific literature. While patients may have perceived symptoms as being related to tramadol, their doctors were not recording most of the symptoms reported to them as side effects. This must have contributed to the low rate of yellow card submissions to the CSM. However given that the majority of symptoms reported by questionnaire were known side effects of tramadol, the results suggest there was significant under-reporting. This is despite the requirement for minor or known ADRs to black triangle drugs to be reported to the CSM.

When the top ten most frequently reported symptoms in the present study were compared with the CSM data using total number of reports as the denominator, higher reporting frequencies were found for six of the top ten symptoms reported in the present study, while lower frequencies were found for three others which were nonetheless among the top ten symptoms reported in CSM data. This may suggest that the patient self-reporting study tended to detect more minor and known side effects as well as background symptoms, i.e. dry mouth, constipation, increased sleep, flushing and unusual tiredness/ weakness, whereas the CSM tended to detect more serious side effects, i.e. nausea/ vomiting, itching of skin, rash, hallucinations, confusion and convulsions. This finding is in agreement with studies by Mitchell et al. (1989, 1994) and van den Bemt et al. (1999) which concluded that patient-self reporting tended to identify established ADRs particularly to new drugs, while reports from health professionals tended to describe rarer and more severe reactions than patient-self reports. A similar finding was found by Cossmann et al. (1997) in that the

most frequently documented adverse effects of tramadol in clinical and PMS studies, i.e. drowsiness, tiredness and dry mouth were noted very infrequently in spontaneous reports since these side effects are normally known and were described in the product information. For established drugs, the CSM requests reports for all serious suspected reactions, including those that are fatal, life-threatening, disabling, incapacitating or which result in or prolong hospitalisation, even if the reactions are well recognised (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 1998; Denman et al., 1988; Anonymous, 1980). However, tramadol is a newer drug with the black triangle symbol for which any reactions should be reported, even those which are minor or well-known. While it may be that doctors did not know the precise meaning of the CSM's black triangle, as was found in a study by Belton et al. (1995), it is most likely that for the patients who did report symptoms, their GPs viewed these as symptoms of disease states, not ADRs. This is confirmed by the documentation of the vast majority of symptoms which were recorded in notes as disease-related. Another reason may be that doctors placed less significance on less serious reactions, resulting in failure to report those reactions to the CSM. As the Yellow Card system (organised by the CSM) is known to suffer from under-reporting (D'Arcy, 1996; Speirs et al., 1994; Walker and Lumley, 1986; Martin et al., 1998), it is not surprising that the present study found greater percentages of overall symptoms reported than those from CSM data.

This study shows that a large number of patients in the community actually suffer from minor side effects, i.e. dry mouth and constipation (32.6% and 24.4% of the total respondents) which were often ignored by health professionals. The results also support the suggestion that an ADR monitoring system based on reports from patients would be cheap and might lead to quicker identification of symptomatic reactions to some new drugs (Mitchell et al., 1988). However, clearly not all symptoms reported by

the patients were likely to be true adverse reactions of tramadol since many symptoms may have related to their disease states or other drugs taken, while 310 were unattributable, suggesting some over-reporting by patients.

It was only possible to compare results to a PEM study by using patient-months during the whole treatment period as a denominator, the same as PEM method, therefore only respondents providing information about duration of therapy were included in this comparison (285 patients). This method of calculation reduced the frequency of the top ten commonly reported symptoms, however all except nausea/ vomiting were reported more frequently than from the PEM data. This may indicate that patient self-reporting tended to detect more known side effects than the PEM method which depends on the willingness of doctors to report events. This method has also encountered an under-reporting problem similar to that seen with the Yellow Card system (Inman and Pearce, 1993). Six of the top ten reported symptoms in the present study were cited among the top 20 events reported of the PEM data. The comparison to PEM data thus supports the suggestion that patient-self reporting did appear to identify potential side effects caused by tramadol. Most of the top 20 reported events of tramadol from PEM data were expected and minor side effects, such as nausea/ vomiting, headache, dizziness, lassitude, insomnia, drowsiness and anxiety which were similar to the findings of the present study. Campbell and Howie (1988) have also commented that the PEM method seemed to fail to detect serious reactions.

Interestingly, the frequency of increased sweating and dizziness/ vertigo reported in the present study were comparable to the CSM data and PEM data, respectively. It is possible that these symptoms bothered patients and were easily identified by patients as side effects of tramadol, thus leading to reports about these side effects to doctors.

Tolerance may have developed to other symptoms, such as nausea/ vomiting, which were found with lower frequency in the present study, compared with the CSM and PEM data. This is especially likely in comparisons to data from PEM reports which concentrate on events occurring in the early months of therapy (Freemantle et al., 1997). Therefore, acute reactions, such as nausea/ vomiting, are more likely to be detected by this method than that used in the present study which asked patients to report any symptoms experienced during the previous 12 months prior to receiving the questionnaire.

Six of the ten most commonly reported symptoms from tramadol in the main study were also among the top ten symptoms reported from co-proxamol in the pilot study. These were dry mouth, constipation, flushing, unusual tiredness/ weakness, itching of skin and dizziness/ vertigo. All are known side effects to both drugs. Although the numbers taking co-proxamol may be too small for accurate comparisons, light-headedness, increased sleep and nausea/ vomiting were found in significantly higher proportions in patients taking tramadol than in those taking co-proxamol. The remaining seven of the top ten commonly reported symptoms were comparable in both drugs. This finding is in line with a meta-analysis of 3453 postoperative patients from 18 studies by Moore and McQuay (1997) which showed that incidence of nausea and vomiting was higher in patients taking an oral single dose of tramadol 50, 75 and 100 mg than in those taking paracetamol 650 mg combined with propoxyphene 100 mg for dental pain. Tramadol was also shown to cause more drowsiness, nausea/ vomiting and dizziness than the combination of paracetamol and propoxyphene for postoperative pain but only at a dose of 100mg. Sunshine (1994) reviewed oral single dose studies of tramadol and found that tramadol at 50, 75 or 100 mg resulted in a higher incidence of nausea/ vomiting, dizziness and headache than the combination of paracetamol (650 mg) and dextropropoxyphene (100 mg) for both dental extraction

and postoperative pain. While the dose of dextropropoxyphene HCl studied here is lower than that studied by those workers and the present study involves chronic therapy, the similar findings are interesting. However, a comparative study of the analgesic efficacy and safety profiles between tramadol and co-proxamol was conducted by Crighton et al. (1997) which demonstrated that the incidence of nausea/ vomiting were comparable which contrasts with the present finding. These researchers did however present a similar trend towards a lower incidence of CNS side effects in co-proxamol group, i.e. drowsiness, dizziness, headache, but no statistical differences were proved.

Data from Drugdex Drug Evaluation Monographs (1998), Moore and McQuay (1997) and Dayer et al. (1994) demonstrated that nausea, vomiting, constipation, dry mouth, fatigue, dizziness, somnolence, headache and sweating are relatively commonly reported adverse effects of tramadol. All except headache were also found in the top ten reported symptoms of the present study. Although headache was not among the top ten symptoms reported, it was reported by a high percentage (n=40, 11.6%) of the respondents. Cossmann et al. (1997) summarised the safety data of tramadol from phase II to IV clinical studies, including postmarketing surveillance studies covering more than 21,000 patients, as well as the spontaneous reporting system. These workers found that the most frequently documented ADRs in clinical and PMS studies were nausea/ vomiting, dizziness, drowsiness, tiredness, sweating and dry mouth which were all found in the top ten reported symptoms of the present study. These comparisons may indicate that patient-self reporting seems to be an effective method for detecting ADRs to new drugs.

Summarising data from clinical trials and postmarketing studies using Drugdex Drug Evaluation Monographs (1998), Sunshine (1994), Cossmann et al. (1997), Budd

(1994), Moore and McQuay (1997), Crighton et al. (1997), Hopkins et al. (1998) and Ruoff (1999) results in an incidence of dry mouth ranging from 3-18%, light-headedness 0.3-1.3%, constipation 1.9-35%, increased sleep 0.3-50%, increased sweating 1.1-20%, nausea/ vomiting 3.1-65%, unusual tiredness/ weakness 5.9-35%, itching of skin 0.1-25% and dizziness/ vertigo 1-25%. By calculating interval incidence estimates for the present study as previously described and comparing these with the incidences from those studies, it was found that the incidence of seven of the top ten symptoms were similar in range to published studies. These were constipation (8.0-24.4%), increased sleep (6.7-20.3%), increased sweating (6.6-20.1%), nausea/ vomiting (6.3-19.2%), unusual tiredness/ weakness (6.2-18.9%) and dizziness/ vertigo (5.3-16.3%) and itching of skin (6.2-18.9%). Two of the top ten symptoms were found in higher incidences in the present study to published data. These were dry mouth (10.7-32.6%) and light-headedness (8.1-24.7%). This again may suggest that patient-self reporting of ADRs is potentially useful and is comparable to other drug monitoring studies. However, it is important to take into consideration the different conditions between studies. For instance, PMS studies were performed in outpatients, whereas most clinical trials are carried out in hospitals. Different methods were also used to detect ADRs, i.e. checklist questionnaire, open questionnaire, interview or observation and also different sample sizes could affect the occurrence of the side effects identified. Light-headedness was found at a higher percentage in this study, possibly because it was carried out in out-patients who are more likely to suffer from hypotension than those in hospitals who were confined to bed. Another explanation is that patients may find it difficult to differentiate light-headedness from dizziness, which could result in a higher incidence of light-headedness and a lower incidence of dizziness. The latter symptom was in fact found in much higher incidence in other studies (up to 35%). Interestingly, dry mouth was the most commonly reported symptom found in the present study, much higher than reported elsewhere. This may

suggest that minor and known ADRs could be detected more often by patient self-reporting, or that symptoms reported with higher frequencies were likely to be caused by concomitant drugs taken or patients' disease states, i.e. there was over-reporting.

The researcher classified the majority of symptoms reported by patients as possibly caused by tramadol (53.4%), with a further 13.8% probably caused by tramadol. Thus, the results showed that greater proportion of the respondents reported symptoms potentially caused by tramadol (67.2%) than those not likely to be caused by tramadol (32.8%). More symptoms reported by respondents prescribed tramadol were classified as 'unlikely' (19.5%) than was found in the remaining drugs (16.4%). One possible reason is that there are fewer known side effects to tramadol than other drugs studied, thus a larger number of symptoms were classified as not being caused by tramadol. Incomplete data provided by respondents may however have affected these classifications.

When the classifications of symptoms reported by 50 patients, whose medical notes were accessed, into four criteria of causal relationship were compared between the expert and the researcher, there was agreement for 69.5% of the total 315 symptoms which indicated a moderate agreement (Kappa = 0.43). Similar levels of agreement have been found in other studies. Using conventional four categories, i.e. definite, probable, possible and doubtful, between-rater agreement for two physicians and four pharmacists who independently assessed 63 selected ADRs was 38-63% (Kappa 0.21-0.4) (Naranjo et al., 1981). Similarly, using the standardised assessment created by Venulet et al. (1980), 391 (61%) of a total 640 ADR reports were identical in the judgement of four evaluators. However, the development of a probability category for assessment resulted in an 83-92% agreement and Kappa = 0.69-0.86 (Naranjo et al., 1981). There is thus broad agreement between several studies that evaluators

frequently disagree in their assessment of ADR reports using their subjective judgement (Koch-Weser et al., 1977; Kramer et al., 1979; Meyboom et al., 1997; Venulet et al., 1980; Naranjo et al., 1981). Venulet (1992) has also suggested that 'the true causality of a single case of ADR is not known and, working retrospectively with a finite amount of data, will never be known'.

Chapter 6

Results and Discussion:

Main study: Venlafaxine

6.1 Results

6.1.1 Response rate and demographic data

There was a total of 633 postal questionnaires sent to patients prescribed venlafaxine. Of these, 263 patients returned valid responses giving a response rate of 41.5%. Of the total respondents, 78 (29.7%) were male and 184 (70.0%) were female, one (0.4%) did not specify. The mean ± SD age of the respondents was 46.6 ± 15.7 years but the majority of patients were aged 40-59 (41.8%) and 20-39 (36.5%). Table 6.1 lists number of the respondents in different age groups.

Table 6.1 Number of respondents prescribed venlafaxine according to age groups

Age group	Number of respondents	%
< 20	1	0.4
20-39	96	36.5
40-59	110	41.8
60-79	40	15.2
≥ 80	10	3.8
not specified	6	2.3
Total	263	100

6.1.2 Drug therapy

The majority of the respondents were taking 1-3 (50.6%) and 4-6 (14.8%) concomitant drugs. The mean ± SD of number of concomitant drugs was 2.4 ± 2.0 (range 0-10) (see Table 6.2). There was not a strong relationship between increasing age and number of concomitant drugs (Spearman r = 0.280, P < 0.001). The average duration of taking venlafaxine was 381.5 days (SD = ± 215.1). The majority of the respondents had been taking venlafaxine for 361-540 days (n=81, 33.9%) and 181-360 days (n=76, 31.8%), followed by 541-720 days (n=34, 14.2%), 1-180 days (n=31, 13.0%) and >720 days (n=17, 7.1%), respectively. Of the total respondents, 99 (11.8%), 411 (49.1%), 198 (23.7%) and 77 (9.2%) were taking venlafaxine one, two, three and four times daily, respectively. The most frequent indication for taking venlafaxine was depression (n=232) with relatively few respondents citing other indications (Table 6.3). One hundred and fifteen respondents (43.7%) reported that they also had other medical conditions. Although 65 respondents (24.7%) reported that they had been in hospital after starting venlafaxine, none of them indicated that the admissions had been caused by venlafaxine. Of the total 86 respondents who had stopped taking venlafaxine, the most frequently cited reasons were that patients felt they did not need the drug any longer 22 (25.6%) and their doctors said they did not need it any longer 19 (22.1%) (Table 6.4). There was a total of 26 respondents (9.9%) who had stopped venlafaxine because either they or their doctors had identified problems with it.

Table 6.2 Number of respondents prescribed venlafaxine according to number of concomitant drugs

Number of concomitant drugs	Number of respondents	%
0	28	10.6
1-3	133	50.6
4-6	39	14.8
7-9	10	3.8
≥10	2	0.8
not specified	51	19.4
Total	263	100

Table 6.3 Number of respondents prescribed venlafaxine according to indication for use

Indication	Number of respondents	%
depression	232	88.2
anxiety	5	1.9
panic attack	1	0.4
stress	6	2.3
other psychotic disorder	5	1.9
myalgic encephalomyelitis	2	0.8
not specified	12	4.6
Total	263	100

Table 6.4 Reasons for stopping venlafaxine cited by 86 respondents

Reason	Number of respondents	%
I felt I didn't need it any longer.	22	25.6
The doctor said I didn't need it any longer.	19	22.1
The doctor told me to stop as I was having problems with it.	16	18.6
I decided to stop as I was having problem with it.	10	11.6
I felt it wasn't helping me	8	9.3
others	11	12.8
Total	86	100

6.1.3 Symptoms reported

Of the total 263 respondents prescribed venlafaxine, 249 (94.7%) reported at least one symptom, while only 14 (5.3%) reported no side effects experienced. There were 97 different symptoms and 2700 total symptoms reported (median = 7, range = 0-71). There was no relationship between increasing age and number of reported symptoms in the respondents prescribed venlafaxine (Spearman r = -0.124, P = 0.047). The number of reported symptoms by respondents in different age groups of the respondents is presented in Figure 6.1. Again, there were no relationships between the number of reported symptoms and increasing number of concomitant drugs (Spearman r = 0.121, P = 0.079) or duration of therapy (Spearman r = 0.088, P = 0.169) (Figure 6.2). Forty nine (18.6%) and 99 (37.6%) of the 263 respondents were taking other antidepressants and other CNS drugs, respectively. There was also no

significant association between the number of symptoms reported and whether patients were taking other antidepressants (χ^2 = 6.139, df = 3, P = 0.105) or other CNS drugs (χ^2 = 1.047, df = 3, P = 0.790).

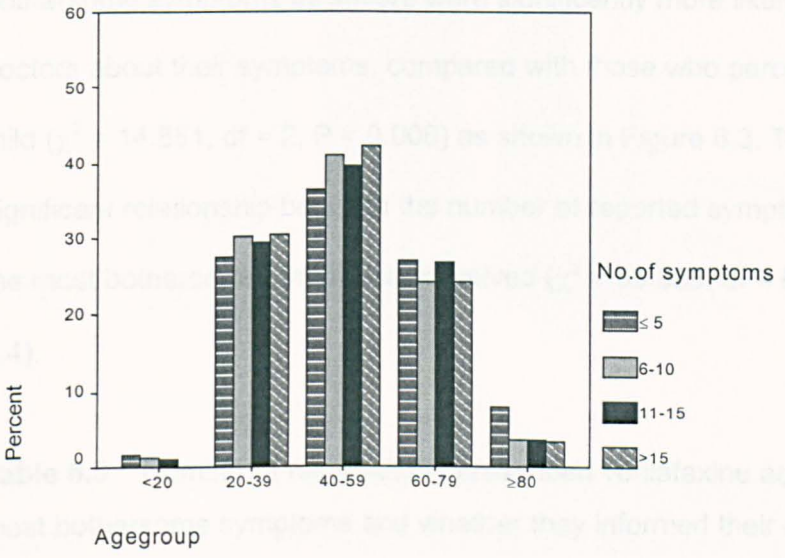

Figure 6.1 Number of reported symptoms by respondents taking venlafaxine in relation to age group

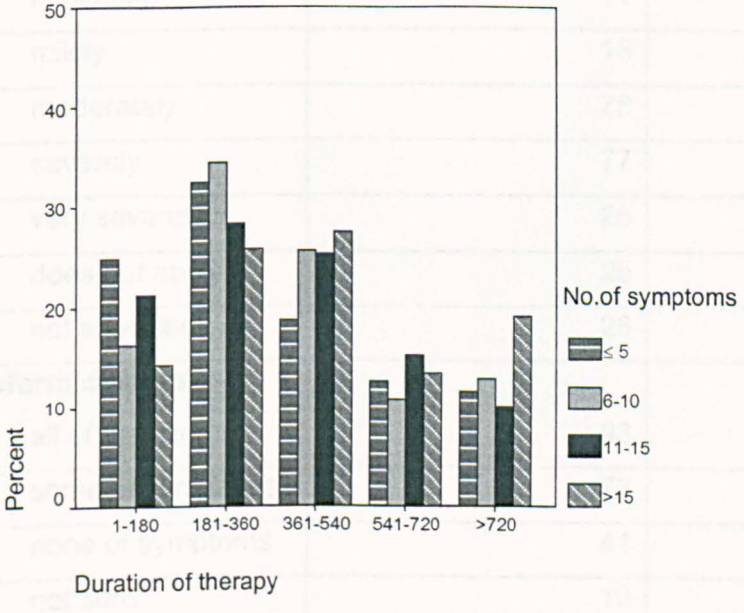

Figure 6.2 Number of reported symptoms by respondents taking venlafaxine in relation to duration of therapy

The majority of respondents perceived the severity of the most bothersome symptoms as moderately (n =78, 29.7%) and severely (n = 77, 29.3%). Thirty five percent of the respondents had informed their doctors of all symptoms reported in the questionnaires and 27.8% had reported some of them (Table 6.5). Patents who perceived the most bothersome symptoms as severe were significantly more likely to have informed their doctors about their symptoms, compared with those who perceived the symptoms as mild (χ^2 = 14.851, df = 2, P = 0.006) as shown in Figure 6.3. There was also a significant relationship between the number of reported symptoms and the severity of the most bothersome symptoms perceived (χ^2 = 33.866, df = 6, P < 0.001) (Figure 6.4).

Table 6.5 Number of respondents prescribed venlafaxine according to severity of most bothersome symptoms and whether they informed their doctors

	Number of respondents	%
Severity		
minimally	11	4.2
mildly	18	6.8
moderately	78	29.7
severely	77	29.3
very severely	26	9.9
does not apply	25	9.5
not specified	28	10.6
Inform doctors		
all of symptoms	93	35.4
some of symptoms	73	27.8
none of symptoms	41	15.6
not sure	19	7.2
does not apply	19	7.2
not specified	18	6.8

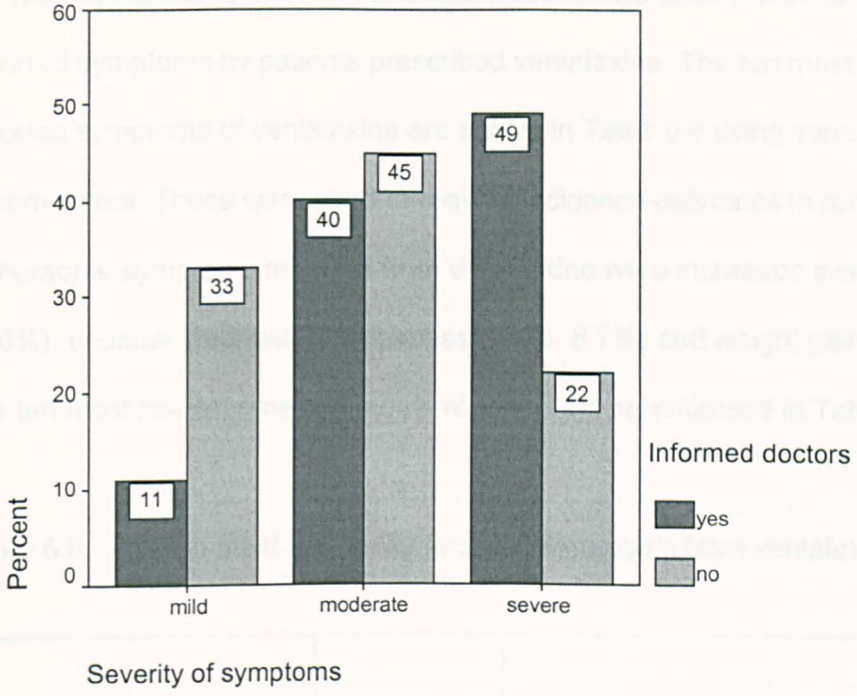

Figure 6.3 Severity of most bothersome symptoms reported by patients prescribed venlafaxine in relation to whether patients reported symptoms to their doctors

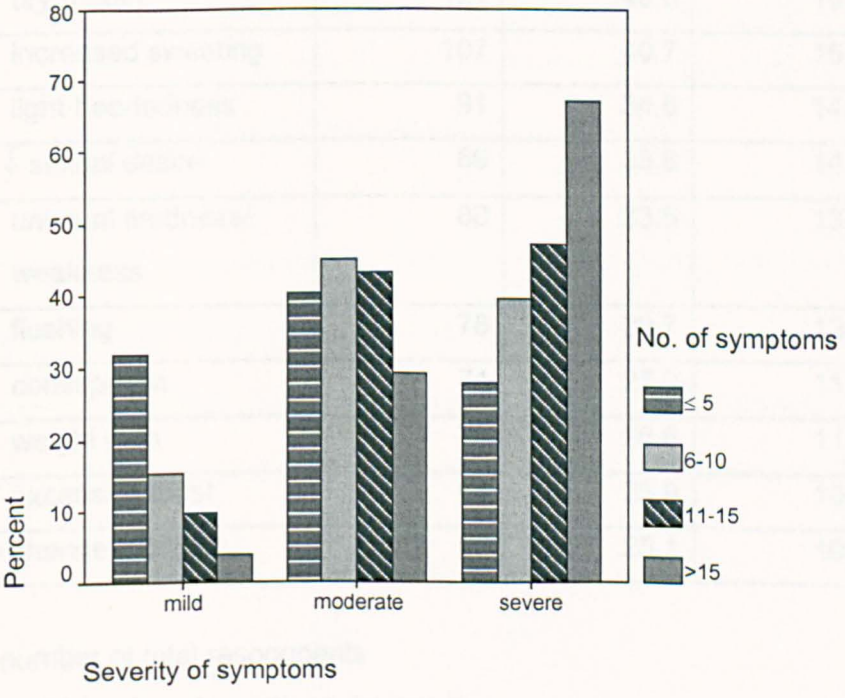

Figure 6.4 Severity of most bothersome symptoms in relation to number of symptoms reported by patients prescribed venlafaxine

Dry mouth, increased sweating and light-headedness were the three most commonly reported symptoms by patients prescribed venlafaxine. The ten most frequently reported symptoms of venlafaxine are shown in Table 6.6 using variety of denominators. These were used to provide incidence estimates in ranges. The most bothersome symptoms reported from venlafaxine were increased sweating (n=41, 15.6%), unusual tiredness or weakness (n=23, 8.7%) and weight gain (n=23, 8.7%). The ten most bothersome symptoms reported are summarised in Table 6.7.

Table 6.6 The ten most frequently reported symptoms from venlafaxine

Rank	Frequency of reported Symptoms	%		
		N = 263*	N = 633**	N = 2700***
1. dry mouth	121	46.0	19.1	4.5
2. increased sweating	107	40.7	16.9	4.0
3. light-headedness	91	34.6	14.4	3.4
4. ↓ sexual desire	89	33.8	14.1	3.3
5. unusual tiredness/ weakness	88	33.5	13.9	3.3
6. flushing	78	29.7	12.3	2.9
7. constipation	71	27.0	11.2	2.6
8. weight gain	70	26.6	11.1	2.6
9. excessive thirst	68	25.9	10.7	2.5
10.change in mood	66	25.1	10.4	2.4

* number of total respondents

** number of total questionnaires sent

*** number of total reported symptoms

Table 6.7 The ten most bothersome symptoms reported by patients prescribed venlafaxine

Rank	Number of patients* (n= 263)	%
1. increased sweating	41	15.6
2. unusual tiredness/ weakness	23	8.7
3. weight gain	23	8.7
3. decrease in sexual desire	16	6.1
5. difficulty concentrating	15	5.7
6. reduction in sleeping	12	4.6
7. anxiety/ agitation	12	4.6
8. constipation	11	4.2
9. nausea/ vomiting	10	3.8
10. dry mouth	10	3.8

* total frequency of most bothersome symptoms = 366

Of the total 86 respondents who discontinued venlafaxine, ten (11.6%) reported a total of 49 symptoms which started after stopping venlafaxine, the most frequent being change in mood (10), dizziness/ vertigo (5) and unusual tiredness/ weakness (5) (Table 6.8). Eight out of the total 17 different symptoms reported were known withdrawal symptoms.

Table 6.8 Frequency of reported symptoms which started after stopping venlafaxine

Symptoms	Frequency of reported symptoms* (%) (n = 86)**
1. unsteadiness on feet	2 (2.3%)
2. headache@	4 (4.6%)
3. decrease in appetite	1 (1.2%)
4. nausea/ vomiting@	4 (4.6%)
5. confusion@	1 (1.2%)
6 light-headedness	2 (2.3%)
7. dizziness/ vertigo@	5 (5.8%)
8. anxiety/ agitation@	4 (4.6%)
9. change in mood	10 (11.6%)
10. anger/ aggression	3 (3.5%)
11. reduction in sleeping@	3 (3.5%)
12. unusual tiredness/ weakness@	5 (5.8%)
13. increased sleep	1 (1.2%)
14. increased sweating@	1 (1.2%)
15. weight loss	1 (1.2%)
16. palpitations	1 (1.2%)
17. flu-like symptoms	1 (1.2%)
Total	49 (57.0%)

* number of patients reporting these symptoms = 10

** number of patients who stopped taking venlafaxine = 86

@ known withdrawal symptoms (total frequency = 27, 31.4%)

6.1.4 Comparison between symptoms reported in the questionnaire and in medical notes

Of the total 401 symptoms reported by 53 patients whose medical notes were studied, only 96 (23.9%) were recorded by GPs in the notes. Of these, 69 (72%) were recorded as symptoms, 24 (25.0%) were recorded as side effects of venlafaxine and three (3%) were recorded as side effects of other drugs taken. Seventeen (32.1%) and 13 (24.5%) of the total 53 respondents reported complete information in the questionnaire about concomitant drugs and disease states, respectively, compared with the records in their medical notes. The ten most commonly reported symptoms in the questionnaire and the frequency with which these were recorded in the medical notes are compared in Table 6.9.

Table 6.9 Comparison of the ten most frequent symptoms of venlafaxine reported by patients in questionnaires with those recorded by doctors in medical notes

Symptom and Rank	Frequency of reported symptoms (n= 53)		% availability in medical notes
	Questionnaires	Medical notes	
1. dry mouth	23	3	13
2. increased sweating	20	11	55
3. light-headedness	14	0	0
4. decrease in sexual desire	21	2	10
5. unusual tiredness/ weakness	11	6	54
6. flushing	14	6	43
7. constipation	14	6	43
8. weight gain	13	8	62
9. excessive thirst	11	0	0
10. change in mood	12	11	92

6.1.5 Comparison between symptoms reported in the present study with CSM data

Of the ten most common symptoms reported by patients prescribed venlafaxine in the present study, only increased sweating was among the ten most commonly reported symptoms in CSM data. Table 6.10 compares the frequency of the ten most frequently reported symptoms in the present study with CSM data together with ranking in number of the most frequently symptoms reported in CSM data. The study data was compared with the CSM data using total frequency of reported symptoms as a denominator. Considering each individual symptom, nine of the ten most commonly reported symptoms in the present study had significantly different proportions from those in CSM data, with only increased sweating being similar (Z = 0.27, 95% CI = -0.87-1.14%, P = 0.785). Increased sweating was in fact the only one of the top ten symptoms in CSM data which was among the top ten reported symptoms in the present study, although unusual tiredness/ weakness and change in mood were within the top 20 CSM symptoms. Similarly, five of the top ten reported symptoms of CSM data had significantly higher frequency than those in the present study. Five symptoms (increased sweating, anxiety/ agitation, tremor, palpitations and paraesthesia) however were reported with similar proportions to the present study (Table 6.11).

Table 6.10 Comparison of the ten most frequently reported symptoms of venlafaxine in the present study with CSM data

Rank	Frequency of reported Symptoms (%)		P-value***	CSM ranking No.
	Own study*	CSM data**		
1. dry mouth	121 (4.5%)	25 (0.8%)	<0.001	23
2. increased sweating@	107 (4.0%)	113 (3.8%)	0.785	5
3. light-headedness	91 (3.4%)	60 (2.0%)	0.002	12
4. ↓ sexual desire	89 (3.3%)	12 (0.4%)	<0.001	>30
5. unusual tiredness/ weakness	88 (3.3%)	34 (1.2%)	<0.001	19
6. flushing	78 (2.9%)	19 (0.6%)	<0.001	>30
7. constipation	71 (2.6%)	28 (0.9%)	<0.001	21
8. weight gain	70 (2.6%)	11 (0.4%)	<0.001	>30
9. excessive thirst	68 (2.4%)	5 (0.2%)	<0.001	>30
10. change in mood	66 (2.4%)	35 (1.2%)	<0.001	18

* denominator = total frequency of reported symptoms = 2700

** denominator = total frequency of reported symptoms = 2956

*** Z-test

@ one of the ten most frequently reported symptoms from CSM data

Table 6.11 Comparison of the ten most frequently reported symptoms of venlafaxine in CSM data with the present study

Rank	Frequency of reported symptoms (%)		P-value***
	CSM data*	Own study**	
1. nausea/ vomiting	334 (11.6%)	64 (2.4%)	<0.001
2. dizziness/ vertigo	173 (5.9%)	48 (1.8%)	<0.001
3. headache	150 (5.1%)	50 (1.9%)	<0.001
4. rashes	145 (4.9%)	15 (0.6%)	<0.001
5. increased sweating@	113 (3.8%)	107 (4.0%)	0.785
6. unsteadiness on feet	91 (3.1%)	41 (1.5%)	<0.001
7. anxiety/ agitation	83 (2.8%)	59 (2.2%)	0.133
8. tremor	79 (2.7%)	56 (2.1%)	0.139
9. palpitations	66 (2.2%)	58 (2.1%)	0.828
10. paraesthesia	65 (2.2%)	46 (1.7%)	0.177

* denominator = total frequency of reported symptoms = 2956

** denominator = total frequency of reported symptoms = 2700

*** Z-test

@ one of the ten most frequently reported symptoms of the present study

6.1.6 Comparison between symptoms reported in the present study and PEM data

Using patient-months as a denominator to facilitate comparison to a PEM study, there were significantly higher proportions of the top ten symptoms reported in the present study, compared with PEM data (Table 6.12). Only unusual tiredness/ weakness was among the top ten reported events of PEM data, however, four of the top ten reported symptoms in this study were cited among the 20 most frequently reported events of PEM data. These were increased sweating, unusual tiredness/ weakness, constipation and change in mood.

Table 6.12 Comparison of the ten most frequently reported symptoms of venlafaxine in the present study with PEM data

Rank	Frequency of reported Symptoms (%)		P-value***
	Own study*	PEM data**	
1. dry mouth	111 (3.58%)	94 (0.17%)	<0.001
2. increased sweating@	99 (3.19%)	185 (0.32%)	<0.001
3. light-headedness	87 (2.80%)	94 (0.17%)	<0.001
4. ↓ sexual desire	85 (2.74%)	26 (0.05%)	<0.001
6 unusual tiredness/ weakness@	84 (2.71%)	355 (0.62%)	<0.001
6. flushing	72 (2.32%)	34 (0.06%)	<0.001
7. constipation@	66 (2.13%)	182 (0.32%)	<0.001
8. weight gain	65 (2.09%)	99 (0.18%)	<0.001
9. excessive thirst	62 (2.00%)	7 (0.01%)	<0.001
10. change in mood@	60 (1.93%)	416 (0.74%)	<0.001

* denominator = total number of patient-months of treatment = 3102 (number of valid patients = 244)
** denominator = total number of patient-months of treatment = 56516
*** Z-test @ one of the 20 most frequently reported events from PEM data

6.1.7 Comparison between symptoms reported in the main study and the pilot study

Symptoms reported to venlafaxine were compared with those reported to the older antidepressants in the pilot study, trazodone and doxepin. Many of the symptoms reported were the same for all three drugs and occurred with similar frequency. However, increased sweating (Z=6.58, 95% CI= 23.43-43.31%, P <0.001) and flushing (Z=3.67, 95% CI = 9.27-30.53%, P <0.001) were reported less frequently with both trazodone and doxepin (Tables 6.13 and 6.14). Four further symptoms were also reported less frequently with doxepin than with venlafaxine. These were light-headedness, reduced sexual desire, unusual tiredness/ weakness and change in mood (Table 6.14).

Table 6.13 Comparison of the ten most frequently reported symptoms of venlafaxine with trazodone

Rank	Frequency of reported Symptoms (%)		P-value**
	Venlafaxine (n=263)	Trazodone* (n=41)	
1. dry mouth@	121 (46.0%)	20 (48.8%)	0.741
2. increased sweating	107 (40.7%)	3 (7.3%)	<0.001
3. light-headedness@	91 (34.6%)	16 (39.0%)	0.588
4. ↓ sexual desire	89 (33.8%)	9 (22.0%)	0.094
5. unusual tiredness/ weakness@	88 (33.5%)	14 (34.1%)	0.931
6. flushing	78 (29.7%)	4 (9.8%)	<0.001
7. constipation@	71 (27.0%)	13 (31.7%)	0.544
8. weight gain	70 (26.6%)	11 (26.8%)	0.977
9. excessive thirst@	68 (25.9%)	12 (29.3%)	0.653
10. change in mood	66 (25.1%)	12 (29.3%)	0.583

* denominator = number of total respondents

** Z-test

@ one of the top ten most frequently reported symptoms of trazodone

Table 6.14 Comparison of the ten most frequently reported symptoms of venlafaxine with doxepin

Rank	Frequency of reported Symptoms (%)		P-value**
	Venlafaxine (n=263)	Doxepin* (n=52)	
1. dry mouth@	121 (46.0%)	26 (50.0%)	0.599
2. increased sweating	107 (40.7%)	4 (7.7%)	<0.001
3. light-headedness@	91 (34.6%)	9 (17.3%)	0.004
4. ↓ sexual desire	89 (33.8%)	7 (13.5%)	<0.001
5. unusual tiredness/ weakness@	88 (33.5%)	9 (17.3%)	0.007
6. flushing	78 (29.7%)	6 (11.5%)	0.001
7. constipation@	71 (27.0%)	9 (17.3%)	0.102
8. weight gain@	70 (26.6%)	9 (17.3%)	0.115
9. excessive thirst@	68 (25.9%)	9 (17.3%)	0.147
10. change in mood	66 (25.1%)	4 (7.7%)	<0.001

* denominator = number of total respondents

** Z-test

@ one of the top ten most frequently reported symptoms of doxepin

6.1.8 Patient attribution of symptoms to drugs

Of the total number of perceived symptoms reported, 1518 (56.2%) were classified by the researcher as being possibly caused by the study drugs, with a further 549 (20.3%) classed as probably caused by study drugs. Three hundred and fifty four symptoms (13.1%) were classed as unlikely to be an ADR and 279 were unattributable (10.3%). Table 6.15 lists the result of the classification for causal relationship of the perceived symptoms according to the eight criteria. The highest frequency was of those symptoms which could be caused by the study drug and concomitant drugs as well as patients' disease states (criteria 4). A higher percentage (76.5%) of the reported symptoms were therefore potentially caused by venlafaxine (probable/ possible) than those (23.5%) not likely to be caused by venlafaxine (unlikely/ unattributable).

Table 6.15 Classification of symptoms reported of venlafaxine classified into eight criteria for assessment of causal relationship

Causal relationship	Criteria	Total frequency of reported symptoms	
		No.	%
Probable ADRs	1	549	20.3
Possible ADRs	2	502	18.6
	3	411	15.2
	4	605	22.4
Subtotal		1518	56.2
Unlikely ADRs	5	72	2.7
	6	161	6.0
	7	121	4.5
subtotal		354	13.2
unattributable ADRs	8	279	10.3
Total		2700	100

6.1.9 Comparison between expert and the researcher opinion on the classification for causal relationship

Of a total 401 symptoms reported by 53 patients whose medical notes were accessed and evaluated, there was agreement for 320 symptoms (79.8%) on the causal relationship, while there was disagreement for 81 symptoms (20.2%) between the expert and the researcher. Considering each criteria of the causal relationship, 1 (0.2%), 274 (68.3%), 32 (8.0%) and 13 (3.3%) of the symptoms reported were mutually agreed with the classifications as probable, possible, unlikely and unattributable, respectively (Table 6.16). Kappa value for agreement between the expert and the researcher was 0.51 indicating moderate agreement (Altman, 1992).

Table 6.16 Comparison of expert and researcher classifications of symptoms reported from venlafaxine into four criteria according to causal relationship

Researcher Classifications	**Number of reported symptoms by expert classifications (%)**				**Total**
	Probable	Possible	Unlikely	Unattributable	
Probable	1 (0.2%)	18 (4.5%)	10 (2.5%)	2 (0.5%)	31 (7.7%)
Possible	0 (0%)	274 (68.3%)	21 (5.2%)	4 (1.0%)	299 (74.6%)
Unlikely	0 (0%)	8 (2.0%)	32 (8.0%)	5 (1.2%)	45 (11.2%)
Unattributable	0 (0%)	5 (1.2%)	8 (2.0%)	13 (3.3%)	26 (6.5%)
Total	1 (0.2%)	305 (76.1%)	71 (17.7%)	24 (6.0%)	401 (100%)

6.2 Discussion

The response rate from patients prescribed venlafaxine (41.5%) was higher than the overall response rate of the main study (36.3%) and for tramadol (32.8%). The proportion of female respondents taking venlafaxine was higher than for tramadol and the overall results of the main study, probably because depression occurs more often in females than males (Lloyd, 1995). The majority of respondents prescribed venlafaxine were younger than those prescribed tramadol. Again this probably reflects the wide age range over which depression is found. The mean number of concomitant drugs was also found to be lower in those taking venlafaxine (2.4, maximum =10 drugs) than the overall results (3.0) and those taking tramadol (3.7, maximum = 16 drugs), however the majority of respondents as with the overall study were taking 1-3 concomitant drugs. This supports the suggestion that older patients, which made up the majority of the tramadol group, may take more medicines than younger patients, as in the venlafaxine group (Cunningham et al., 1997; Classen et al., 1997; Lee, 1993; May, 1997). However, as in the pilot study, the relationship between increasing age and number of concomitant drugs in respondents taking venlafaxine was not strong.

About 34% of the respondents had taken venlafaxine for 361-540 days with the mean duration of therapy being 381.5 days which was slightly longer than those taking tramadol (majority = 1-180 days, mean = 324.8 days). This is probably a reflection of the need for prolonged therapy for depression. Nearly ten percent of respondents were taking venlafaxine more than three times a day which is in excess of the dose recommendation of two to three times a day (Feighner, 1994). However, the licensed dose regimen in the UK is 75-150 mg daily in 2 divided doses (British Medical Association and the Royal Pharmaceutical Society of Great Britain, 1998). It is

possible that some patients could not remember the exact dosage regimen of the medicines taken or may have confused venlafaxine with concomitant drugs taken.

As anticipated, most of the respondents were taking venlafaxine for depressive illness (88.2%), but only 4.2% were taking venlafaxine for anxiety and stress. This differs from the pilot study in which fewer respondents were taking trazodone (68%) and doxepin (60%) for depression and more were taking trazodone (29%) and doxepin (33%) for other indications, such as anxiety, sleeplessness or panic attack. Thus older drugs, for which more information and experience are available, appeared to be used in more diverse indications than newer drugs. Less than 50% of the respondents stated that they had other medical conditions. This again may be a consequence of the majority of patients being aged less than 60 years, therefore they were less likely to have other diseases than the elderly, although it is possible that some patients were not aware of or concerned about other health problems. There were no patients admitted to hospital as a result of adverse reactions to venlafaxine. This may suggest that venlafaxine seemed to cause few serious ADRs likely to require hospitalisation in an out-patient sample. Danjou and Hackett (1995) also found that severe or serious events occurred at a relatively low rate in venlafaxine-treated patients, in particular, the rates of deaths, seizures, severe rash and elevated liver function test were low. This is also supported by Ellingrod and Perry (1994), who showed that venlafaxine had a very low rate of occurrence of serious, rare effects, compared with other antidepressants. However, venlafaxine is a newly marketed drug, thus more information on its safety profile must be provided from further PMS studies before making this assumption. The sample size of the present study may not be sufficient for detecting serious ADRs, particularly rare ones. In pre-marketing studies, about 500-3000 patients are required for detecting ADRs which occur in 1-6 persons per thousand of exposed individuals (O' Donnell, 1994).

Forty one (15.6%) respondents had stopped taking the drug because their disease had improved whereas 26 (9.9%) perceived problems which caused them to discontinue the drug with or without their doctor 's recommendation. This is comparable to the discontinuation rate (8-10%) found in long term treatment (up to one year) in controlled studies as summarised by Danjou and Hackett (1995). On the other hand, these workers found that short term treatment (six weeks) with venlafaxine resulted in a higher rate of discontinuation due to its adverse effects, representing 16%, while a greater incidence (19-20%) of discontinuing treatment due to side effects was found in clinical trial studies reported by Ellingrod and Perry (1994) and in the analysis of pooled studies by Feighner (1994). However, the data from the present study showed that the average duration of taking venlafaxine was 382 days, thus it is comparable to long term treatment. The percentage of the respondents who had discontinued venlafaxine was higher than in similar studies by Fisher et al. (1995) which found 5.1% of patients stopped sertraline and 2.1% of patients stopped fluoxetine because of their side effects. This may be due to the slightly different methodological approach, although both methods detected ADRs by patient self-reporting. However it could suggest that venlafaxine caused more serious side effects which patients were unable to tolerate than sertraline and fluoxetine. Only eight respondents (3%) indicated that they stopped venlafaxine as it was not helping them. This is a very low figure compared to that found by Danjou and Hackett (1995) who showed that 7-11% of venlafaxine-treated patients discontinued the drug due to unsatisfactory response. While this may be an indicator that venlafaxine is an effective antidepressant, the study was not designed to assess efficacy.

Nearly 95% of the respondents taking venlafaxine reported at least one symptom which was higher than those in the overall results (88.6%) and those taking tramadol (84.0%). The respondents also reported a wide ranger of symptoms (0 – 71) and

higher number of different symptoms (97) compared to tramadol, with the median of number of symptoms reported being seven. This may due to biases from some patients who over-reported symptoms which they suffered regardless of whether the symptoms were caused by venlafaxine or not. It may also suggest that patients taking antidepressants tended to experience more different side effects than those taking analgesics. As was found in the tramadol group, there was no positive relationship between increasing age, number of concomitant drugs or duration of therapy with the number of symptoms reported by respondents taking venlafaxine. The lack of a clear relationship between increasing age and number of reported symptoms was confirmed by an analysis of a clinical trial database by Rudolph and Derivan (1996), indicating there was no significant difference in the risk of occurrence of the most common ADRs was revealed between those over and under 65 years. Likewise, the number of reported symptoms did not differ depending on whether patients were taking other antidepressants or other CNS drugs. The lack of an effect of other CNS drugs differs from that found in the tramadol group which may be due to a lower average number of concomitant drugs being taken by respondents on venlafaxine.

Severity ratings for the most bothersome symptoms reported were provided by 80% of the respondents on venlafaxine, which was higher than the average of the remaining study drugs (65%). This is probably associated with the finding that a smaller number of respondents on venlafaxine (5%) reported no side effects experienced than the rest study drugs (14%), therefore this led fewer patients on venlafaxine to tick less 'does not apply' and 'unspecified'. A greater proportion of venlafaxine respondents perceived the most bothersome symptoms as moderately and severely than was found for tramadol respondents. This could be due to the longer duration of therapy in venlafaxine respondents, which would consequently increase exposure time to the drug and the possibility of perceiving more severe side effects. As with the pilot study

and the tramadol respondents, increased severity of the most bothersome symptoms was associated with an increase in the number of reported symptoms and increased tendency to inform their doctors about the symptoms reported. Interestingly, 63% of respondents informed their doctors about the symptoms reported in the questionnaires which they thought to be side effects from venlafaxine. This was more than those on tramadol, which could also be related to the greater number reporting severe symptoms.

Six of the symptoms cited as being most bothersome by the respondents taking venlafaxine were also among the top ten most frequently reported. These were dry mouth, constipation, increased sweating, unusual tiredness or weakness, decrease in sexual desire and weight gain. This showed that patients tended to report symptoms, even minor side effects, which more bothered or interfered with their lifestyle. All of the ten most bothersome symptoms reported and nine of the ten most frequently symptoms reported, except change in mood, are known side effects of venlafaxine. Therefore the respondents seemed to report mostly symptoms potentially caused by venlafaxine, as was found with tramadol. However, change in mood, which could be attributed to patient illness, was also cited as one of the top ten symptoms reported and also featured among symptoms reported after stopping the drug. Such reports are probably similar to the inclusion of bone and joint pain among symptoms reported with tramadol. This suggests that, while the majority of symptoms reported by patients are perceived side effects of medicines, the questionnaire may also have prompted the reporting of disease-related symptoms. There were in total 6.0% of the symptoms reported which were classed as explainable only by disease states present and many more (42.1%) could have been related to either disease states or drug therapy. Fewer respondents prescribed tramadol reported symptoms of disease states (4.5% plus 25.1% related to disease states or drugs), which may reflect the ease with which

symptoms can be distinguished from potential ADRs to analgesics. However it must be taken into consideration that incomplete data was provided by those respondents whose medical records were examined, which therefore leads to the assumption that most of the remaining respondents did not provide all information about concomitant drugs and disease states. This would have an effect on the classification of symptoms reported.

Twelve percent of the 86 respondents who stopped venlafaxine reported symptoms which started after stopping the drug. Nearly 50 percent of the total 17 different symptoms reported were known withdrawal symptoms caused by venlafaxine, such as headache, nausea/ vomiting, confusion and dizziness. This is in line with reports of withdrawal symptoms occurring on abrupt cessation, dose reduction or tapering of venlafaxine which were more frequent at daily doses of 150 mg or more (Sinclair et al., 1998). The symptoms are in agreement with a review by Sinclair et al. (1998) which summarised that the common withdrawal symptoms were headache, nausea, vomiting, dizziness, insomnia, nervousness and asthenia. Interestingly, the most frequently reported symptom after discontinuing venlafaxine was change in mood, which is not a known withdrawal reaction and is more likely to relate to patients' depressive illness, which recurred after discontinuing their treatment. This explanation could also apply to the other symptoms reported which are not known withdrawal symptoms, such as decrease in appetite, anger/ aggression, increased sleep, weight loss and palpitations. It is also possible that these and other symptoms, i.e. light-headedness, unsteadiness on feet and flu-like symptoms may be related to other disease states or concomitant drugs which patients were still taking after discontinuing venlafaxine.

Similarly low recording in medical notes of symptoms reported by patients taking venlafaxine in the questionnaires (23.9%) was found to the tramadol group and the pilot study. However a larger proportion of these (25%) were recorded as side effects than was found in the tramadol group. This may be due to doctors' greater awareness of venlafaxine side effects or the greater severity of the symptoms, as was found in patient reports. It is of interest that for 11 of the 12 patients who reported change in mood, this symptom which was recorded in medical notes, although as a symptom related to depressive illness. Many patients had clearly identified this effect in their questionnaires. Increased sweating and weight gain were also documented in more than half the cases who reported these symptoms by questionnaire. It appears that these were bothersome to the patients, leading them to report the symptoms to their doctors. This is supported by frequent citation of these among the most bothersome symptoms reported (rank 1 and 3).

The comparison of patient-reported symptoms to data from CSM reports suggest that patient self-reporting tended to detect more minor and known side effects such as dry mouth, constipation, flushing, unusual tiredness/ weakness and excessive thirst, whereas the CSM method tended to detect more serious and acute side effects such as nausea/ vomiting, rashes, unsteadiness on feet and dizziness/ vertigo. This was also found in the tramadol group and is in agreement with other work (Mitchell et al., 1989, 1994; van den Bemt et al., 1999). While the symptoms reported most frequently differed, five of the top ten CSM reports were found with similar frequency in the present study. Also there may have been difficulty in distinguishing light-headedness, reported in the questionnaire, from dizziness, vertigo or unsteadiness on feet, which were frequent among CSM reports.

Surprisingly, change in mood, which was frequently reported in the present study and would appear unlikely to be attributed to an adverse reaction of venlafaxine was ranked 18 among CSM reports. Change in mood was also among the top 20 reported events in PEM data. This may suggest that even health professionals may report symptoms associated with patients' illness rather than the suspected drug. This could be due to difficulty in distinguishing the disease states from the reaction caused by the suspected drug cited as one of the main reasons for ADR under-reporting (Randhawa and Smith, 1987; Scott et al., 1987; Generali et al., 1995; Bateman et al., 1992). It is also possible that mood changes bothered patients, thus led them to report it to their doctors. Alternatively, it is possible that these could represent side effects of venlafaxine, since the drug can cause mania/ hypomania or suicidal ideation (Stoner et al., 1999), although thought of suicide was also included in the questionnaire. However in a study of 2258 venlafaxine-treated patients, the incidence of both of these side effects was remarkably low (0.4% each) (Danjou and Hackett, 1995), while there were 25.1% of patients in the current study reporting mood change. Thus, it would seem most likely that the majority of patient reports would have been related to depressive illness.

In total four of the top ten reported symptoms in the present study were also among the top 20 events reported from PEM data, many of which were known side effects of venlafaxine. PEM data generally identified less severe side effects than CSM data, such as increased sweating, unusual tiredness, insomnia, drowsiness and constipation which is similar to the findings of the present study.

Nausea/ vomiting, dizziness and headache were found less frequently in the present study, compared with the CSM and PEM data. This is likely to be due to tolerance developing among the respondents (Danjou and Hackett, 1995; Sinclair et al., 1998;

Feighner, 1994; Preskorn, 1995) which is also demonstrated by PEM data showing that 69.6% of all nausea/ vomiting events were reported during the first month of therapy, falling rapidly over the subsequent weeks. PEM studies are more likely to detect acute reactions than the present method, since they concentrate on events in the early months of therapy (Freemantle et al., 1997). Preskorn (1995) also commented that the incidence of side effects did not reflect their severity as some adverse effects were either intolerable or so serious that treatment must be discontinued. This is in line with the finding of the present study that nausea/ vomiting was one of top ten most bothersome symptoms but not one of the ten most common reported symptoms.

Excessive thirst and decrease in sexual desire were found in considerably higher frequencies in the present study, compared with CSM and PEM data. This may be because the patients in the present study who ticked dry mouth often ticked excessive thirst as well, while the reports from health professionals may have been more likely to cite only dry mouth. It is also likely that side effects concerning confidential issues, such as sexual life are much more likely to be detected by a patient-self reporting method since reports to doctors are likely to be infrequent.

Many of the ten most commonly reported symptoms from venlafaxine were also among the top ten symptoms reported from trazodone and doxepin, all of which were previously known side effects to both drugs. Although numbers of respondents on the older drugs were low, therefore comparisons should be undertaken cautiously, there were no significant differences in the incidences of anticholinergic side effects between the three drugs. This supports the findings of Holliday and Benfield (1995), Ellingrod and Perry (1994) and Danjou and Hackett (1995), who compared venlafaxine and trazodone. However it differs from the conclusions of Sinclair et al. (1998) and

Augustin et al. (1997), who suggested that venlafaxine caused much fewer anticholinergic side effects than tricyclic antidepressants, of which doxepin is an example. Dry mouth was, in fact, the most commonly reported symptom from venlafaxine. It is possible that this could be due to a lack of tolerance developing, as suggested by Feighner (1994). Increased sweating was found with much higher frequency in patients receiving venlafaxine and was also among common symptoms reported in clinical studies (Sinclair et al., 1998; Danjou and Hackett, 1995), although the latter workers did not identify this as being more frequent with venlafaxine than trazodone. Unusual tiredness was found in similar proportions between venlafaxine and trazodone, which has also been found elsewhere (Ellingrod and Perry, 1994; Danjou and Hackett, 1995).

Many of the symptoms reported in the present study with high frequencies (see Appendix J) were among those identified from other sources (Drugdex Drug Evaluation Monographs, Holliday and Benfield, Feighner, Danjou and Hackett, Preskorn, Augustin et al., Ellingrod and Perry, Sinclair et al.) as commonly reported adverse effects of venlafaxine. While the frequencies of these reported symptoms were high in the present study, the estimates of lowest likely incidence obtained using number of questionnaires issued as a denominator correlate well with the incidences reported in these studies for five common symptoms. It may thus be that the method, while identifying mainly potential adverse events, does result in over-estimates of their incidence. The majority of the symptoms reported were classed as potentially caused by venlafaxine (76.5%), which was slightly higher than those reported from tramadol (67.2%). Thus although there were more symptoms reported in total from venlafaxine and also a wider range of symptoms, this is likely to be due to there being more potential side effects with this drug than is the case with tramadol. Most of the classification of 401 symptoms reported by a sample of 53 patients were agreed by an

independent expert (320, 80%), of which 275 (86%) were judged to be probable or possible ADRs. If it is assumed that the classification was therefore generally appropriate, the questionnaire appears to have demonstrated a reasonable specificity for adverse effects to venlafaxine. This is further supported by the general finding that patients who reported few symptoms were less likely to report those classed as unlikely or unattributable ADRs.

Chapter 7

Results and Discussion:

Main study: Other drugs

7.1 Results of anticonvulsants

7.1.1 Response rates and demographic data

There were total 115, 40 and 23 postal questionnaires sent to patients prescribed gabapentin, lamotrigine and topiramate, respectively. Of these, 68, 18 and 13 patients responded giving response rates of 59%, 45% and 56% for gabapentin, lamotrigine and topiramate, respectively. Of the total respondents prescribed these three anticonvulsants, 45 (45%) were male and 43 (54%) were female, one (1.0%) did not specify. The mean ± SD age of the total respondents was 38.1± 14.1 years with the majority of patients in the age groups 20-39 (50%) and 40-59 (31%). Regarding each individual drug, patients taking gabapentin had mean age ± SD = 39.8 ± 15.0, lamotrigine had mean age ± SD = 30.8 ± 9.5 and topiramate had mean age ± SD = 39.2 ± 12.6. Table 7.1 lists number of the respondent characteristics according to sex and age groups.

Table 7.1 Number of respondents prescribed gabapentin, lamotrigine and topiramate according to sex and age groups

	Number of respondents (%)			
	Gab* (n=68)	**Lam*** (n=18)	**Top*** (n=13)	**Total** (n=99)
Sex				
Male	33 (49%)	6 (33%)	6 (46%)	45 (45%)
Female	34 (50%)	12 (67%)	7 (54%)	53 (54%)
not specified	1 (1%)	-	-	1 (1%)
Age group *				
< 20	5 (7%)	2 (11%)	-	7 (7%)
20-39	29 (44%)	13 (72%)	7 (54%)	49 (50%)
40-59	22 (32%)	3 (17%)	6 (46%)	31 (31%)
60-79	9 (13%)	-	-	9 (9%)
≥ 80	1 (1%)	-	-	1 (1%)
not specified	2 (3%)	-	-	2 (2%)

* Gab = Gabapentin, Lam = Lamotrigine, Top = Topiramate

7.1.2 Drug therapy

The majority of the respondents were taking 1-3 (75%) and 4-6 (14%) concomitant drugs. The overall mean ± SD of number of concomitant drugs was 2.7 ± 1.6 (range 1-8) with no differences between the patient groups (Table 7.2). The average duration of taking the anticonvulsants was 720.1 days (SD = ± 574.5). The majority of the respondents had been taking anticonvulsants for more than 720 days (n=32, 40%). Figure 7.1 shows duration of therapy for each drug. Of the total respondents prescribed anticonvulsants, 29 (37%), 36 (46%) and 13 (17%) were taking these one,

two, three or more times daily, respectively. Indications for use reported in the questionnaires are listed in Table 7.3. There were 46 (46%) respondents who reported having other medical conditions. Although 42 respondents (42%) reported that they had been in hospital since starting the study anticonvulsants, none of them indicated that the admissions were caused by those drugs. Five respondents had stopped taking their study anticonvulsants, but only one of these, taking topiramate, had done so because they were having a problem with it.

Table 7.2 Number of respondents prescribed gabapentin, lamotrigine and topiramate according to number of concomitant drugs

Number of concomitant drugs	Number of respondents (%)			
	Gab* (n=68)	Lam* (n=18)	Top* (n=13)	Total (n=99)
0	-	-	-	-
1-3	51 (75%)	12 (67%)	11 (84%)	74 (75%)
4-6	11 (16%)	2 (11%)	1 (8%)	14 (14%)
7-9	3 (4%)	2 (11%)	1 (8%)	6 (6%)
≥10	-	-	-	-
not specified	3 (4%)	2 (11%)	-	5 (5%)
mean ± SD	2.7 ± 1.5	2.9 ± 2.2	2.6 ± 1.6	2.7 ± 1.6

* Gab = Gabapentin, Lam = Lamotrigine, Top = Topiramate

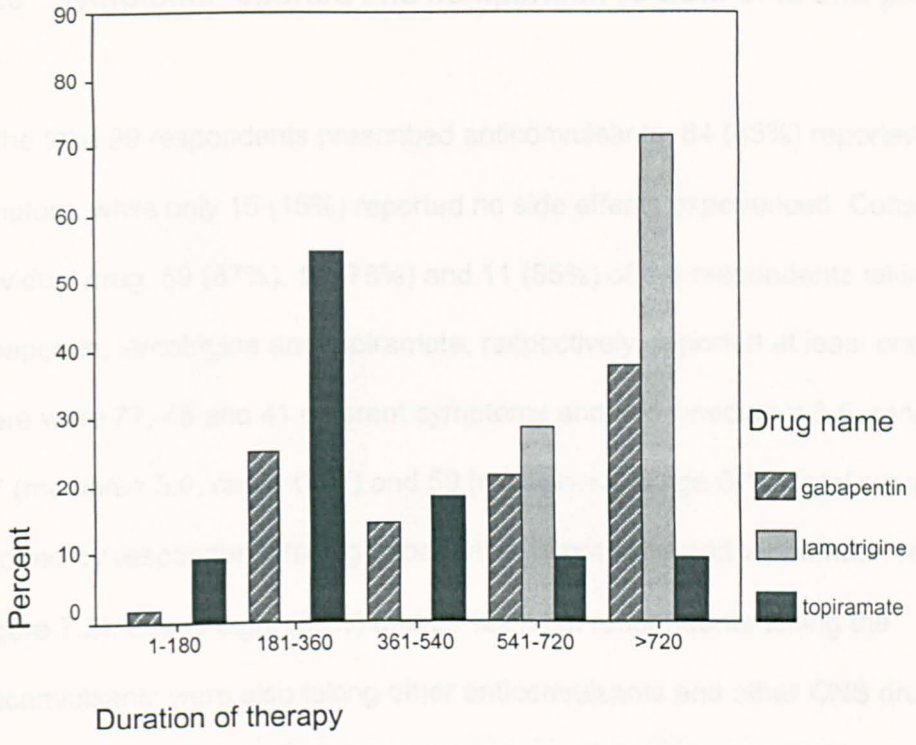

Figure 7.1 Duration of therapy for each anticonvulsant

Table 7.3 Number of respondents prescribed gabapentin, lamotrigine and topiramate according to indication for use

Indication	Number of respondents (%)			
	Gab* (n=68)	**Lam*** (n=18)	**Top*** (n=13)	**Total** (n=99)
unspecified epilepsy	61 (90%)	15 (83%)	13 (100%)	89 (90%)
grand mal epilepsy	1 (1%)	-	-	1 (1%)
partial seizure	4 (6%)	2 (11%)	-	6 (6%)
not specified	2 (3%)	1 (6%)	-	3 (3%)

*Gab = Gabapentin, Lam = Lamotrigine, Top = Topiramate

7.1.3 Symptoms reported and comparison to CSM data and pilot study

Of the total 99 respondents prescribed anticonvulsants, 84 (85%) reported at least one symptom, while only 15 (15%) reported no side effects experienced. Considering each individual drug, 59 (87%), 14 (78%) and 11 (85%) of the respondents taking gabapentin, lamotrigine and topiramate, respectively, reported at least one symptom. There were 77, 46 and 41 different symptoms and 575 (median = 5.5, range 0-37), 117 (median = 5.0, range 0-17) and 59 (median =3, range 0-12) total symptoms reported by respondents taking gabapentin, lamotrigine and topiramate, respectively (Figure 7.2). Eighty eight (89%) and 21 (21%) of respondents taking the anticonvulsants were also taking other anticonvulsants and other CNS drugs, respectively. There were no strong relationships between number of reported symptoms and increasing number of concomitant drugs (Spearman r = 0.061, P = 0.557), duration of therapy (Spearman r = 0.103, P = 0.360) or age (Spearman r = 0.215, P = 0.034). While no significant association was found between number of symptoms reported and the presence of other anticonvulsants (P = 0.482, Fisher's exact test), patients taking other CNS drugs were more likely to report more than ten symptoms (χ^2 = 14.412, df = 1, P <0.001) (Table 7.4).

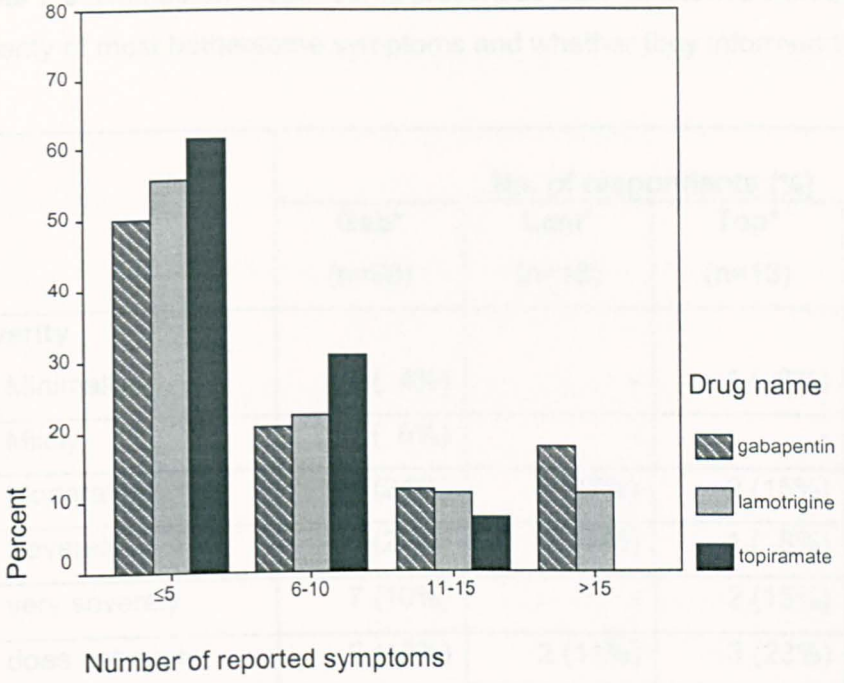

Figure 7.2 Number of reported symptoms for each anticonvulsant

Table 7.4 Presence of other CNS drugs in relation to number of patients reporting symptoms

Presence of other CNS drugs	Number of patients (%)		
	Number of reported symptoms		Total*
	≤10	>10	
No	61 (83.6%)	12 (16.4%)	73 (100%)
Yes	9 (42.9%)	12 (57.1%)	21 (100%)

* Total number of valid cases = 94

The majority of respondents perceived the severity of the most bothersome symptoms as moderately (n =21, 21%) and severely (n = 24, 24%). Thirty six percent of the respondents had informed their doctors about all symptoms reported in the questionnaires and a further 24 % about some of these symptoms (Table 7.5).

Table 7.5 Number of respondents prescribed each anticonvulsant according to severity of most bothersome symptoms and whether they informed their doctors

	No. of respondents (%)			
	Gab* (n=68)	**Lam*** (n=18)	**Top*** (n=13)	**Total** (n=99)
Severity				
Minimally	3 (4%)	-	1 (8%)	4 (4%)
Mildly	4 (6%)	-	-	4 (4%)
Moderately	16 (24%)	3 (17%)	2 (15%)	21 (21%)
Severely	15 (22%)	8 (445)	1 (8%)	24 (24%)
very severely	7 (10%)	-	2 (15%)	9 (9%)
does not apply	9 (13%)	2 (11%)	3 (23%)	14 (14%)
not specified	14 (21%)	5 (28%)	4 (31%)	23 (23%)
Inform doctors				
all of symptoms	26 (38%)	4 (22%)	6 (46%)	36 (36%)
some of symptoms	18 (26%)	5 (28%)	1 (8%)	24 (24%)
none of symptoms	4 (6%)	2 (11%)	3 (23%)	9 (9%)
not sure	2 (3%)	1 (6%)	-	3 (3%)
does not apply	11 (16%)	2 (11%)	1 (8%)	14 (14%)
not specified	7 (10%)	4 (22%)	2 (15%)	13 (13%)

*Gab = Gabapentin, Lam = Lamotrigine, Top = Topiramate

Weight gain, loss of memory and anxiety/ agitation were the most commonly reported symptoms from gabapentin (Table 7.6) while loss of memory (8 patients), difficulty in concentrating (6) and light-headedness (5) were those from lamotrigine. The most frequently reported symptoms from topiramate were weight loss, bloated feeling and unsteadiness on feet (3 patients each). The most common bothersome symptom reported for gabapentin was weight gain (11), for lamotrigine was loss of memory (5) and for topiramate was unusual tiredness/ weakness (2). Carbamazepine and sodium valproate, the anticonvulsants involved in the pilot study, were compared with the

three in the main study (Table 7.6). Many symptoms were common to all the drugs. While the numbers of respondents in all groups are relatively low, the data do suggest that weight gain may be more of a problem with gabapentin than with the other drugs and that difficulty concentrating, loss of memory, increased sleep or unusual tiredness/ weakness are common side effects with all five anticonvulsants.

Table 7.6 Frequently reported symptoms of the anticonvulsants in main study and pilot study

Symptom	Frequency of reported Symptoms (%)				
	Gab* (n=68)	Lam* (n=18)	Top* (n=13)	Car* (n=44)	Val* (n=25)
1. weight gain	24 (35%)	4 (22%)	1 (7.7%)	5 (11%)	6 (24%)
2. loss of memory	21 (31%)	8 (44%)	2 (15%)	8 (18%)	9 (36%)
3. anxiety/ agitation	17 (25%)	1 (6%)	1 (8%)	4 (9%)	6 (24%)
4. change in mood	17 (25%)	4 (22%)	1 (8%)	4 (9%)	6 (24%)
5. difficulty concentrating	17 (25%)	6 (33%)	3 (23%)	10 (23%)	9 (36%)
6. increased sleep	16 (24%)	3 (17%)	2 (15%)	15 (34%)	8 (32%)
7. headache	16 (24%)	2 (11%)	2 (15%)	7 (16%)	6 (24%)
8. unsteadiness on feet	14 (21%)	4 (22%)	3 (23%)	6 (14%)	5 (20%)
9. dry mouth	14 (21%)	1 (6%)	1 (8%)	7 (16%)	4 (16%)
10. light-headedness	14 (21%)	5 (28%)	1 (8%)	9 (20%)	4 (16%)
11. dizziness/ vertigo	14 (21%)	4 (22%)	2 (15%)	8 (18%)	3 (12%)
12. unusual tiredness/ weakness	13 (19%)	3 (17%)	2 (15%)	12 (27%)	14 (56%)
13. tremor	13 (19%)	4 (22%)	1 (8%)	9 (20%)	11 (44%)
14. reduction in sleeping	8 (12%)	4 (22%)	-	6 (14%)	4 (16%)

*Gab = Gabapentin, Lam = Lamotrigine, Top = Topiramate, Car = Carbamazepine, Val = Sodium valproate

Of the ten most commonly symptoms reported by patients taking gabapentin in the present study, five were cited as the ten most commonly reported symptoms in CSM data. These were anxiety/ agitation, change in mood, increased sleep, headache and unsteadiness on feet (Table 7.7). However, only unsteadiness on feet and dizziness/ vertigo from lamotrigine, both reported by four patients in the present study, were among the top ten symptoms of CSM data. Weight loss and unsteadiness on feet, the commonest symptoms from topiramate were cited in 22 and 12 out of 203 CSM reports, respectively.

Table 7.7 Comparison of the ten most frequently reported symptoms of gabapentin in the present study with CSM data

Rank	Frequency of reported symptoms (%)	
	Own study (n= 575)*	**CSM data** (n= 583)*
1. weight gain	24 (4.2%)	11 (1.9%)
2. loss of memory	21 (3.7%)	4 (0.7%)
3. anxiety/ agitation@	17 (3.0%)	15 (2.6%)
4. change in mood@	17 (3.0%)	15 (2.6%)
5. difficulty concentrating	17 (3.0%)	1 (0.2%)
6. increased sleep@	16 (2.8%)	32 (5.5%)
7. headache@	16 (2.8%)	23 (3.9%)
8. unsteadiness on feet@	14 (2.4%)	29 (5.0%)
9. dry mouth	14 (2.4%)	1 (0.2%)
10. light-headedness	14 (2.4%)	--

* total frequency of reported symptoms

@ one of the 10 most frequently reported symptoms of CSM data

7.2 Results of other antidepressants

7.2.1 Response rates and demographic data

There were in total 204, 132 and 48 postal questionnaires sent to patients prescribed nefazodone, citalopram and moclobemide, respectively. The response rates were 31.4% (n=64), 32.6% (n=43) and 33.3% (n=16) for nefazodone, citalopram and moclobemide, respectively. Of the total respondents prescribed these three antidepressants, 37 (30.1%) were male and 85 (69.1%) were female, one (0.8%) did not specify. The mean ± SD age of the total respondents was 49.0 ± 14.9 years with the majority of patients in the age groups 40-49 (48.0%) and 20-39 (26.0%). Regarding each individual drug, respondents prescribed nefazodone had mean age ± SD = 46.2 ± 11.8, citalopram had mean age ± SD = 55.0 ± 18.2 and moclobemide had mean age ± SD = 44.1 ± 11.3. Table 7.8 shows the respondent characteristics according to sex and age groups.

Table 7.8 Number of respondents prescribed nefazodone, citalopram and moclobemide according to sex and age groups

	Number of respondents (%)			
	Nef* (n=64)	**Cit*** (n=43)	**Moc*** (n=16)	**Total** (n=123)
Sex				
Male	25 (39.1)	9 (20.9)	3 (18.8)	37 (30.1)
Female	39 (60.9)	33 (76.7)	13 (81.2)	85 (69.1)
not specified	-	1 (2.3)	-	1 (0.8)
Age group *				
< 20	-	-	-	-
20-39	18 (28.1)	7 (16.3)	7 (43.8)	32 (26.0)
40-59	36 (56.2)	16 (37.2)	7 (43.8)	59 (48.0)
60-79	9 (14.1)	14 (32.6)	2 (12.5)	25 (20.3)
≥ 80	-	5 (11.6)	-	5 (4.1)
not specified	1 (1.6)	1 (2.3)	-	2 (1.6)

* Nef = Nefazodone , Cit = Citalopram, Moc = Moclobemide

7.2.2 Drug therapy

The majority of the respondents were taking 1-3 (51.2%) and 4-6 (22.0%) concomitant drugs. The overall mean ± SD of number of concomitant drugs was 2.4 ± 2.0 (range 1-10) (Table 7.9). The average duration of taking the antidepressants was 353.5 days (SD = ± 300.2). The majority of the respondents were taking the three antidepressants 180-360 days (n=42, 38.9%) and 1-180 days (n=27, 25.0%), followed by 361-540 days (n=17, 15.7%), 541-720 days (n=11, 10.2%) and more than 720 days (n=11,10.2%), respectively. Figure 7.3 presents duration of therapy for each drug. Of the total 123 respondents prescribed the three antidepressants, 40 (32.5%), 74 (60.2%) and 7

(5.7%) were taking them one, two, three or more times daily, respectively. Indications for use reported in the questionnaires are listed in Table 7.10.

Table 7.9 Number of respondents prescribed nefazodone, citalopram and moclobemide according to number of concomitant drugs

Number of concomitant drugs	Number of respondents (%)			
	Nef* (n=64)	Cit* (n=43)	Moc* (n=16)	Total (n=123)
0	7 (10.9)	4 (9.3)	2 (12.5)	13 (10.6)
1-3	34 (53.1)	22 (51.2)	7 (43.8)	63 (51.2)
4-6	10 (15.6)	11 (25.6)	6 (37.5)	27 (22.0)
7-9	1 (1.6)	1 (0.8)	-	2 (1.6)
≥10	-	1 (0.8)	-	1 (0.8)
not specified	12 (18.8)	4 (3.2)	1 (6.2)	17 (13.8)
mean ± SD	1.9 ± 1.7	2.7 ± 2.2	2.9 ± 1.9	2.4 ± 2.0

* Nef = Nefazodone, Cit = Citalopram, Moc = Moclobemide

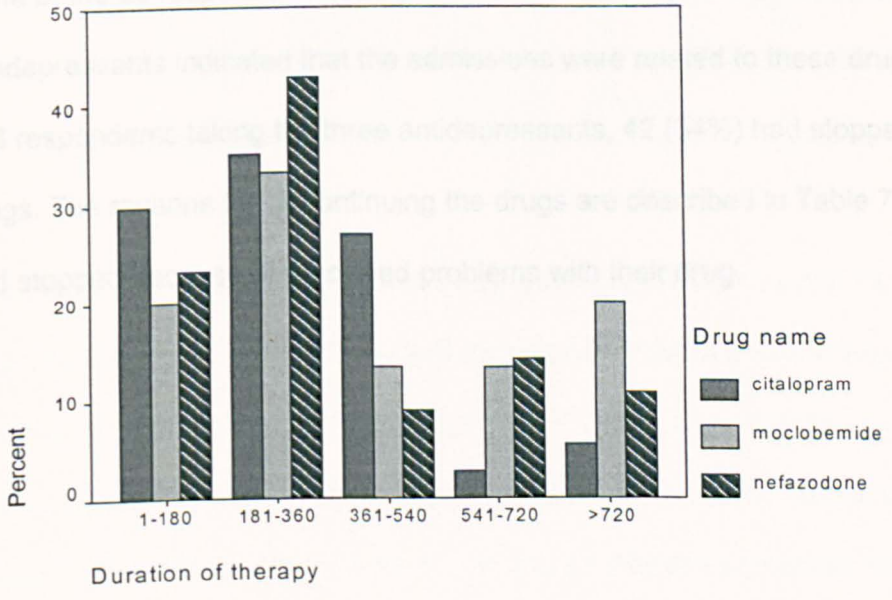

Figure 7.3 Duration of therapy for each antidepressant

Table 7.10 Number of respondents prescribed nefazodone, citalopram and moclobemide according to indication for use

Indication	Number of respondents (%)			
	Nef* (n=64)	**Cit*** (n=43)	**Moc*** (n=16)	**Total** (n=123)
depression	53 (83%)	36 (84%)	14 (88%)	103 (84%)
anxiety	4 (6%)	2 (5%)	-	6 (5%)
panic attack	1 (2%)	-	-	1 (1%)
stress	4 (6%)	1 (2%)	-	5 (4%)
other psychotic disorders	1 (2%)	1 (2%)	-	2 (2%)
other bone or muscle diseases	1 (2%)	-	-	1 (1%)
not specified	-	3 (7%)	2 (12%)	5 (4%)

* Nef = Nefazodone, Cit = Citalopram, Moc = Moclobemide

There were 67 (54%) respondents who reported having other medical conditions. None of the 28 respondents (23%) who reported a hospital admission after starting the antidepressants indicated that the admissions were related to these drugs. Of the total 123 respondents taking the three antidepressants, 42 (34%) had stopped taking the drugs. The reasons for discontinuing the drugs are described in Table 7.11. In total 14 had stopped because of perceived problems with their drug.

Table 7.11 Number of respondents according to reasons for stopping nefazodone, citalopram and moclobemide

Reason	Number of respondents (%)			
	Nef* (n=24)	Cit* (n=13)	Moc* (n=5)	Total (n=42)
I felt I didn't need it any longer.	5 (21%)	4 (31%)	2 (40%)	11 (26%)
The doctor said I didn't need it any longer.	3 (12%)	1 (8%)	-	4 (10%)
The doctor told me to stop as I was having problems with it.	5 (21%)	3 (23%)	-	8 (19%)
I decided to stop as I was having problem with it.	4 (17%)	1 (8%)	1 (20%)	6 (14%)
I felt it wasn't helping me	3 (12%)	3 (23%)	2 (40%)	8 (19%)
Others	4 (17%)	1 (8%)	-	5 (12%)

* Nef = Nefazodone, Cit = Citalopram, Moc = Moclobemide

7.2.3 Symptoms reported and comparison to CSM data and other antidepressants

Of a total 123 respondents prescribed the antidepressants, 114 (92.7%) reported at least one symptom, while only nine (7.3%) reported no side effects experienced. Considering each individual drug, 62 (97%), 37 (86%) and 15 (94%) out of a total respondents taking nefazodone, citalopram and moclobemide, respectively, reported at least one symptom. There were 85, 78 and 52 different symptoms and 677 (median = 8.5, range 0-39), 358 (median = 5.0, range 0-37) and 103 (median = 6.5, range 0-16) total symptoms reported by respondents taking nefazodone, citalopram and

moclobemide, respectively (Figure 7.4). Twenty four (20%) and 43 (35%) of the 123 respondents were taking other antidepressants and other CNS drugs, respectively. There was no relationship between number of reported symptoms and age (Spearman r = -0.132, P = 0.150), number of concomitant drugs (Spearman r = 0.018, P = 0.885) or duration of therapy (Spearman r = -0.011, P = 0.909). Respondents taking other antidepressants were more likely to report more than ten symptoms (χ^2 = 4.140, df = 1, P = 0.042) (Table 7.12), while there was no similar effect of taking other CNS drugs (χ^2 = 0.107, df = 1, P = 0.743).

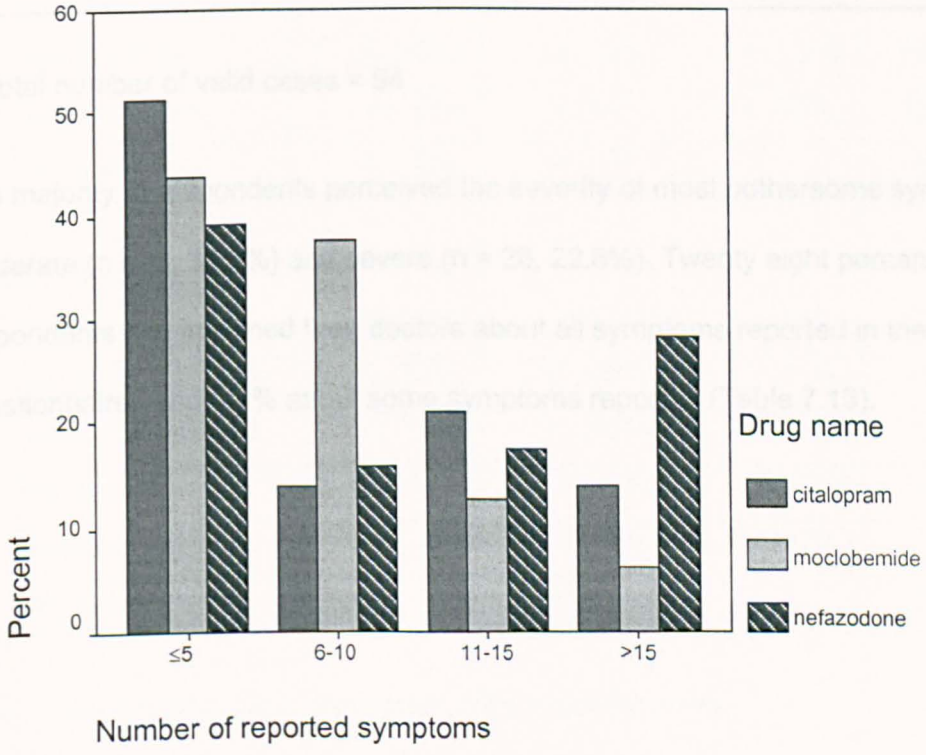

Figure 7.4 Number of reported symptoms for each antidepressant

Table 7.12 Presence of other antidepressants in relation to number of patients reporting symptoms

Presence of other antidepressants	Number of patients (%)		
	Number of reported symptoms		Total*
	≤10	>10	
No	43 (61%)	27 (39%)	70 (100%)
Yes	9 (38%)	15 (62%)	24 (100%)

* Total number of valid cases = 94

The majority of respondents perceived the severity of most bothersome symptoms as moderate (n =38, 30.9%) and severe (n = 28, 22.8%). Twenty eight percent of the respondents had informed their doctors about all symptoms reported in the questionnaires and 30 % about some symptoms reported (Table 7.13).

Table 7.13 Number of respondents prescribed each antidepressant according to severity of most bothersome symptoms and whether they informed their doctors

	Number of respondents (%)			
	Nef* (n=64)	**Cit*** (n=43)	**Moc*** (n=16)	**Total** (n=123)
Severity				
minimally	3 (5%)	2 (5%)	3 (19%)	8 (6%)
mildly	9 (14%)	7 (16%)	2 (12%)	18 (15%)
moderately	19 (30%)	15 (35%)	4 (25%)	38 (31%)
severely	21 (33%)	5 (12%)	2 (12%)	28 (23%)
very severely	6 (9%)	4 (9%)	1 (6%)	11 (9%)
does not apply	5 (8%)	6 (14%)	4 (25%)	15 (12%)
not specified	1 (2%)	4 (9%)	-	5 (4%)
Inform doctors				
all of symptoms	21 (33%)	9 (21%)	4 (25%)	34 (28%)
some of symptoms	22 (34%)	10 (23%)	5 (31%)	37 (30%)
none of symptoms	10 (16%)	10 (23%)	3 (19%)	23 (19%)
not sure	5 (8%)	5 (12%)	2 (12%)	12 (10%)
does not apply	4 (6%)	7 (16%)	2 (12%)	13 (11%)
not specified	2 (3%)	2 (5%)	-	4 (3%)

* Nef = Nefazodone, Cit = Citalopram, Moc = Moclobemide

Dry mouth was clearly the most common symptom for all drugs and constipation and light-headedness were also frequently reported by all respondents except those on moclobemide (Table 7.14). Unusual tiredness/ weakness and increased sleep were also commonly reported to all drugs. Although the number of respondents taking moclobemide was very small, this drug did appear to show a different adverse effect profile, indicated by the proportionately high number of patients reporting headache.

Paraesthesia was a particularly frequent report from respondents on nefazodone and decreased sexual desire was more common in those taking nefazodone and venlafaxine.

Three of the top ten symptoms reported to the CSM for nefazodone were among the top ten in this study (Table 7.15). Nausea/ vomiting was the most frequent symptom reported to the CSM from moclobemide, comprising 80 reports, followed by headache with 63 reports. These symptoms were reported by three and five patients respectively in the present study. Headache, tremor, increased sweating and anxiety/ agitation were found with citalopram in both the present study and reports to the CSM (Table 7.16), although nausea/ vomiting, the commonest symptom among CSM reports was only cited by eight respondents. Unusual tiredness/ weakness, paraesthesia and anxiety/ agitation were also reported frequently in this study to nefazodone, as in CSM data. Difficulty concentrating was reported by 20 patients on nefazodone and was also cited by nine as being most bothersome. Anxiety/ agitation was similarly cited frequently as most bothersome (8 patients) and in general (16 patients). Increased sweating (5) and unusual tiredness/ weakness (5) were cited most frequently as bothersome symptoms with citalopram, while decrease in sexual desire (2) was only the most bothersome symptom reported by patients taking moclobemide.

Table 7.14 Frequency of reported symptoms to the antidepressants in main study and pilot study

Symptom	Frequency of reported Symptoms %					
	Nef (n=64)	**Cit** (n=43)	**Moc** (n=16)	**Ven** (n=263)	**Tra** (n=41)	**Dox** (n=52)
1. dry mouth	29 (45%)	16 (37%)	6 (38%)	121 (46%)	20 (49%)	26 (50%)
2. unusual tiredness	24 (38%)	14 (33%)	3 (19%)	88 (34%)	14 (34%)	9 (17%)
3. light-headedness	22 (34%)	15 (35%)	1 (6%)	91 (35%)	16 (39%)	9 (17%)
4. difficulty concentrating	20 (31%)	3 (7%)	3 (19%)	59 (22%)	13 (32%)	7 (14%)
5. ↓ sleep	19 (30%)	7 (16%)	4 (25%)	64 (24%)	8 (20%)	4 (8%)
6. paraesthesia	19 (30%)	7 (16%)	1 (6%)	46 (18%)	7 (17%)	7 (14%)
6. ↓ sexual desire	17 (27%)	10 (23%)	3 (19%)	89 (34%)	9 (22%)	6 (12%)
8. dizziness/ vertigo	17 (27%)	6 (14%)	4 (25%)	48 (18%)	10 (24%)	6 (12%)
9. tremor	16 (25%)	13 (30%)	1 (6%)	56 (21%)	10 (24%)	4 (8%)
10. anxiety/ agitation	16 (25%)	9 (21%)	2 (12%)	59 (22%)	19 (46%)	4 (8%)
11. ↑ sleep	12 (19%)	14 (33%)	2 (12%)	45 (17%)	17 (42%)	10 (19%)
12. ↑ sweating	10 (16%)	12 (28%)	2 (12%)	107 (41%)	3 (7%)	4 (8%)
13. headache	15 (23%)	11 (25%)	5 (31%)	50 (19%)	2 (5%)	5 (10%)
14. flushing	10 (16%)	10 (23%)	-	78 (30%)	4 (10%)	6 (12%)
15. constipation	11 (17%)	8 (19%)	1 (6%)	71 (27%)	13 (32%)	9 (17%)
16. nausea/ vomiting	14 (22%)	8 (19%)	3 (19%)	64 (24%)	1 (2%)	1 (2%)

Nef = Nefazodone, Cit = Citalopram, Moc = Moclobemide, Ven = Venlafaxine, Tra = Trazodone, Dox = Doxepin

Table 7.15 Comparison of the ten most frequently reported symptoms of nefazodone in the present study with CSM data

Rank	Frequency of reported symptoms (%)	
	Own study (n= 677)*	**CSM data** (n= 1941)*
1. dry mouth	29 (4.3%)	20 (1.0%)
2. unusual tiredness/ weakness@	24 (3.5%)	56 (2.9%)
3. light-headedness	22 (3.2%)	20 (1.0%)
4. difficulty concentrating	20 (3.0%)	9 (0.5%)
5. reduction in sleeping	19 (2.8%)	20 (1.0%)
6. paraesthesia@	19 (2.8%)	76 (3.9%)
7. ↓ sexual desire	17 (2.5%)	3 (0.2%)
8. dizziness/ vertigo@	17 (2.5%)	193 (9.9%)
9. tremor	16 (2.4%)	22 (1.1%)
10. anxiety/ agitation	16 (2.4%)	40 (2.1%)

* total frequency of reported symptoms

@ one of the ten most frequently reported symptoms from CSM data

Table 7.16 Comparison of the ten most frequently reported symptoms of citalopram in the present study with CSM data

Rank	Frequency of reported symptoms (%)	
	Own study (n= 358)*	**CSM data** (n= 731)*
1. dry mouth	16 (4.5%)	13 (1.8%)
2. light-headedness	15 (4.2%)	9 (1.2%)
3 increased sleep	14 (3.9%)	8 (1.1%)
4. unusual tiredness/ weakness@	14 (3.9%)	15 (2.0%)
5. tremor@	13 (3.6%)	30 (4.1%)
6. increased sweating@	12 (3.4%)	24 (3.3%)
7. headache@	11 (3.1%)	34 (4.6%)
8. flushing	10 (2.8%)	1 (0.1%)
9 ↓ sexual desire	10 (2.8%)	6 (0.8%)
10. anxiety/ agitation@	9 (2.5%)	26 (3.6%)

* total frequency of reported symptoms

@ one of the ten most frequently reported symptoms from CSM data

7.3 Results of fentanyl patch

Only eight of the 64 patients (13%) prescribed fentanyl patch who were sent questionnaires returned them. None of these cited cancer pain as the indication for use, although seven described pain in varying types. All eight respondents reported symptoms, giving a total of 94 symptoms, with a median of 12.5 (range 2-24). In total 47 different symptoms were reported, with constipation being the most common (5),

followed by nausea/ vomiting (4), decreased appetite (4) and weight loss (4). Nausea/ vomiting was also among the top ten symptoms reported to the CSM for fentanyl patch (11 out of 327 reports), although constipation was reported only once. Bronchospasm was more frequently reported to the CSM (15 reports) and difficulty in breathing was reported by three of the eight patients in the present study. Despite the very small number of respondents on fentanyl patch, the incidence of reports of constipation and nausea/ vomiting appears to be higher than with tramadol and co-proxamol.

7.4 Patient attribution of symptoms to drugs

Of a total 1303, 4600 and 2727 symptoms reported, 788 (60.5%), 2496 (54.3%) and 1425 (52.3%) were classified by the researchers as being possibly caused by the study drugs, with a further 120 (9.2%), 844 (18.3%) and 367 (13.5%) classed as probably caused by all anticonvulsants, antidepressants and analgesics, respectively, in both main study and pilot study. Two hundred and eighty nine symptoms (17.8%), 755 (16.4%) and 575 (21.0%) were classed as unlikely to be an ADR and 106 (8.1%), 505 (11.0%) and 360 (13.2%) were classed as unattributable from all anticonvulsants, antidepressants and analgesics, respectively. Table 7.17 shows the results of the classification for causal relationship of the perceived symptoms according to the eight criteria for the three different therapeutic groups of drugs including pilot study. The highest frequency was of those symptoms which could have been caused by the study drug and concomitant drugs as well as patients' disease states (criteria 4) for the anticonvulsants (35.8%) and the antidepressants (22.2%), while for analgesics, more symptoms were reported which could have been caused by the study drug and concomitant drugs (criteria 2) (32.2%). Higher percentages of reported symptoms were found to be potentially caused by the study drugs (probable/ possible) in all

therapeutic classes than those not likely to be caused by the study drugs (unlikely/ unattributable) (Table 7.17). Overall, symptoms reported by patients taking antidepressants were more often classed as potentially caused by study drugs, while symptoms reported by patients taking analgesics were more likely to be classed as unlikely to be caused by study drugs and unattributable.

Table 7.17 The overall distribution of symptom class for the three different therapeutic groups of drugs included in the pilot study

Causal relationship	Criteria	Total frequency of reported symptoms (%)		
		Anticonvulsants	Antidepressants	Analgesics
probable ADRs	1	120 (9.2%)	844 (18.3%)	367 (13.5%)
possible ADRs	2	198 (15.2%)	789 (17.2%)	878 (32.2%)
	3	124 (9.5%)	685 (14.9%)	95 (3.5%)
	4	466 (35.8%)	1022 (22.2%)	452 (16.6%)
Subtotal		788 (60.5%)	2496 (54.3%)	1425 (52.3%)
unlikely ADRs	5	121 (9.3%)	159 (3.5%)	260 (9.5%)
	6	68 (5.2%)	355 (7.7%)	157 (5.7%)
	7	100 (7.7%)	241 (5.2%)	158 (5.8%)
Subtotal		289 (22.2%)	755 (16.4%)	575 (21.0%)
unattributable ADRs	8	106 (8.1%)	505 (11.0%)	360 (13.2%)
Total		1303 (100%)	4600 (100%)	2727 (100%)

7.5 Discussion

The overall response rate for patients prescribed anticonvulsants (55.6%) was comparable to the response rate of the anticonvulsants in the pilot study (51.9%). Proportions of female respondents were slightly higher overall than males, however this was mainly due to a larger number of female respondents taking lamotrigine. Similar to the pilot study, the majority of the respondents taking anticonvulsants were aged 20-39 and 40-49. The mean number of concomitant drugs being taken was also similar to the anticonvulsants in the pilot study (2.7 vs 2.4). Nearly 40% of the respondents had taken the anticonvulsants for more than 720 days with the mean duration of therapy of 720 days which was longer than those taking the antidepressants (273 days) and the analgesics (329 days). This is most likely due to the need for continuing long term therapy in patients with epilepsy. Those on anticonvulsants were also more likely to be taking other drugs as the same indication with study drugs (89%) than was the case in patients taking antidepressants (19%) and analgesics (60%).

Almost all respondents were taking anticonvulsants in the main study for epilepsy (97%) as was found in those taking sodium valproate, while a number of patients were taking carbamazepine (in the pilot study) for other conditions (13%) including manic depression and trigeminal neuralgia. Less than 50% of the respondents stated that they had other medical conditions, which could be related to their relatively young age.

Only 5 (5%) respondents had stopped taking the anticonvulsants in the main study. Of these, only one patient had stopped topiramate because of its side effects, which represented 7.7% (1 in 13) of the total respondents taking topiramate. In double-blind,

placebo-controlled trials involving more than 500 patients taking topiramate, the withdrawal rate due to adverse effects was found to be 11-14% (Privitera, 1997; Jones, 1998). The lower rate found in the present study is most likely due to small sample numbers and the likelihood of not the method identifying those who withdrew within the first few months of therapy, which was the most likely period for withdrawal (Privitera, 1997). The very small number who discontinued drugs because of problems may suggest that anticonvulsants seemed to be well-tolerated. Handforth and Treiman (1994) and Ramsay (1994) both found that adverse effects related to gabapentin were not severe and seldom caused drug discontinuation. A recent review by Jones (1998) also found that to date, no evidence was found of serious systematic side effects, such as rash, hepatotoxicity or cardio-toxicity in patients taking topiramate. Nevertheless, Goa and Sorkin (1993) summarised that around 3-11.5% gabapentin-treated patients withdrew from premarketing trials and placebo-controlled trials due to its side effects. Also, Fitton and Goa (1995) suggested that approximately 4-15 % of patients on lamotrigine withdrew from therapy due to its side effects. Other findings have also showed 7-9% withdrawal rates due to adverse effects from lamotrigine (Patsalos and Sander, 1994; Kalviainen, 1993; Messenheimer, 1995; Richens, 1994).

Approximately 85% of the respondents taking the three black triangle anticonvulsants reported at least one symptom, which is lower than the 93% in the pilot study. More patients on gabapentin reported at least one symptom (87%) than for other anticonvulsants and also reported the greatest number of different symptoms (77). A summary of data from long-term studies of gabapentin by Ramsay (1994) found that 81.4% of patients reported at least one symptom. In addition, the US Gabapentin Study Group (1994) concluded that adverse reactions were reported by 88% of patients on gabapentin.

As was found for all study drugs, the respondents tended to rate the most bothersome symptoms as moderate or severe which may be due to the questionnaire design requesting ratings only for the most bothersome symptoms. Messenheimer (1995) and Goa and Sorkin (1993) demonstrated that most ADRs to gabapentin and lamotrigine were of mild to moderate severity. Patients taking other centrally acting drugs were more likely to report more symptoms, in contrast to those taking venlafaxine and other antidepressants. This may be due to a different range of side effects occurring with anticonvulsants compared to other CNS drugs.

Nine of the ten most frequently reported symptoms of gabapentin were expected side effects, except light-headedness, which may not have been distinguished from dizziness, a known side effect. Three of the top ten symptoms from lamotrigine, light-headedness, change or difficulty in hearing and decrease in sexual desire, were not established side effects. It is possible that change in hearing may relate to epilepsy, while decrease in sexual desire could be related to depression which is an established side effect, although the small numbers make interpretation difficult. Overall, patients appeared to report mostly known side effects from the anticonvulsants which is in agreement with the findings from the rest of the study.

There were a number of symptoms reported in the present study which were also cited in CSM data. Six of the top ten symptoms of gabapentin in the present study were among the top ten from CSM data, while only two of the top ten symptoms reported from lamotrigine and three from topiramate were among the top ten symptoms from CSM data. However the small number of sample sizes for the latter two drugs (lamotrigine =18, topiramate =13) mean the results are not representative.

There were also many common side effects with the older anticonvulsants, carbamazepine and sodium valproate, and most reports were of previously known side effects. While the majority of symptoms were reported in patients taking gabapentin, weight gain was particularly frequent. This may suggest that gabapentin was not better tolerated than carbamazepine, which supports the suggestion by Mattson (1995a) that carbamazepine usually produced minimal adverse effects with long term therapy. However, a study comparing the neuropsychological performance of patients taking gabapentin and carbamazepine showed that the effects of both drugs did not differ to a statistically significant degree (Kalviainen et al., 1993) and in the present study similar frequencies were found in difficulty concentrating. In contrast to a review by McLean (1995) which suggested central side effects of gabapentin began within the first few weeks of therapy and lasted for approximately two weeks, in the present study, with the majority of patients (about 75%) taking gabapentin for more than 720 days, there were still a large number of reports of CNS side effects. Patsalos and Sander (1994) and Handforth and Treiman (1994) also demonstrated that weight gain had been reported in some patients, particularly in long term treatment.

A review by Mattson (1995b) found that the overall success rate based on continuation on drugs was better for lamotrigine monotherapy than carbamazepine monotherapy due to its improved tolerability. The numbers in the present study were unfortunately too small to allow comparisons. In addition, the majority of the respondents (89%) were also taking other anticonvulsants in present study which could have affected the reports.

The same problem occurred with topiramate. However, the three reports of weight loss with this drug concord with the high number of reports to the CSM and represented a

higher frequency than that with carbamazepine and sodium valproate. This is in agreement with a review by Privitera (1997).

Data from Drugdex Drug Evaluation Monographs (1998), Kalviainen et al. (1993), Patsolos and Sander (1994), McLean (1995), Ramsay (1994), The US Gabapentin Study Group (1994) and Handforth and Treiman (1994) demonstrated that dizziness, somnolence, ataxia, headache, fatigue, weight gain, nystagmus, tremor, diplopia, nausea/ vomiting and rhinitis are relatively common reported adverse effects of gabapentin. Some of these symptoms were also found in the top ten reported symptoms of the present study. Incidence estimates obtained using different denominators as in Chapters 5 and 6 of increased sleep, unsteadiness on feet, dry mouth and dizziness in the present study were comparable with data from PMS studies and clinical trials, but weight gain, anxiety/ agitation and headache were found in higher percentages. This again supports the suggestion that patient-reporting seems to be a good method for detecting ADRs, although there may be over-reporting of symptoms which are of more concern to patients, such as weight gain, anxiety/ agitation. Interestingly, data from Drugdex database showed that jitteriness and loss of memory led patients to discontinue gabapentin. The number of respondents taking lamotrigine and topiramate were too small to enable useful comparisons to the literature to be made.

The overall response rate for patients prescribed the three antidepressants (43.3%) was comparable to response rate of those in the pilot study (42.3%) with the proportion of female respondents twice that of males and a preponderance of relatively young respondents, as with venlafaxine. Respondents were taking other drugs with the similar frequency to venlafaxine (2.4, range 0-10) though the mean

duration of therapy was less. As with venlafaxine, the indications were limited in comparison to the older drugs.

A high proportion (34%) of respondents on these newer antidepressants had stopped taking the drugs, as was found with venlafaxine. Similar proportions had stopped because of problems either with or without their doctors' suggestion. For nefazodone, this rate (14%) was similar to a comparative trial which included 2496 nefazodone-treated patients and found that about 16% of patients discontinued therapy due to adverse effects (Cyr and Brown, 1996). A multicentre double-blind comparison study in 105 out-patients receiving nefazodone also found a withdrawal rate of 14% (Baldwin et al., 1996), while Robinson et al. (1996) summarised that 12% of 1310 patients taking nefazodone in short-term, placebo-controlled trials worldwide stopped treatment because of adverse experiences. While a slightly higher withdrawal rate (19%) was found by Feiger et al. (1996), no withdrawals (0%) were found by Feighner et al. (1989). The withdrawal rate from citalopram adverse effects in the present study was 9%, which is slightly higher than the 5% found in a meta-analysis of 325 patients (Milne and Goa, 1991). Data from respondents treated with moclobemide was insufficient to draw any conclusions, however studies have found that few patients discontinued the drug due to adverse effects (Fitton et al., 1992; Larsen et al., 1984).

The high proportion (93%) of respondents taking nefazodone, citalopram and moclobemide who reported at least one symptom is similar to that found in patients taking venlafaxine (95%). The frequency for nefazodone (97%) concords with a study by Feiger et al. (1996) which found 96% of a total 78 patients taking nefazodone reported an adverse event during the study period, although fewer patients reported adverse events (84%) in a comparison study by Baldwin et al.(1996). Ninety four

percent of the respondents taking moclobemide in the present study reported at least one symptom, compared to 57% found in a long term study (Moll et al., 1994). Although similar proportions of patients on all the newer antidepressants were also taking other antidepressants, for venlafaxine, there was no increase in symptoms reported, while there was an increase in symptoms reported by those patients who were prescribed nefazodone, citalopram and moclobemide. This may be an effect of sample size.

Most of the ten most frequently reported symptoms were expected side effects, although some could be attributable to depressive illness as well, such as unusual tiredness, headache, reduction in sleeping and anxiety/ agitation which is in agreement with a review by Milne and Goa (1991). This was also found with the venlafaxine group, suggesting that these patients appeared to report symptoms in the questionnaires which interfered with their lifestyle, including those which were attributable to their illness, such as decrease in sexual desire and difficulty concentrating. This is endorsed by the finding that almost all of the most bothersome symptoms reported for antidepressants were among the ten most frequently reported symptoms.

Although the patient numbers were small, there were some interesting reports which compared well with CSM data including the identification of paraesthesia with nefazodone and nausea/ vomiting and headache with moclobemide. Dry mouth, unusual tiredness and increased sleep were frequently reported to all antidepressants, although dry mouth was less frequently reported in the nefazodone group compared with trazodone, which concords with a review by Cyr and Brown (1996). Insomnia was also higher from nefazodone, as was found by these workers. In contrast however with the data from Cyr and Brown (1996), in the present study, dizziness was found with

higher frequency, while anxiety/ agitation were found in lower frequency in the nefazodone group, compared to the trazodone group. No direct comparisons were found in the literature between nefazodone and doxepin, although Robinson et al. (1996), Preskorn (1995) and Fontaine (1993) showed that patients receiving nefazodone experienced a lower frequency of fatigue, postural hypotension, dry mouth, tremor and dizziness than those with imipramine, but a higher frequency of light-headedness. Similar incidences of dry mouth, increased sleep and constipation were found with nefazodone and doxepin in the present study, while the remainders were found in higher percentages in the nefazodone group. This may be related to different tolerability profiles of doxepin and imipramine.

While patients taking citalopram reported a lower frequency of dry mouth than those taking trazodone and doxepin, it was still the most common symptom. However, a meta-analysis of double-blind studies comparing citalopram with tricyclic antidepressants concluded that citalopram appeared to cause relatively fewer anticholinergic side effects (Milne and Goa, 1991). Tremor, increased sweating and headache were found more frequently in patients on citalopram than in those on doxepin. This finding contrasts with a meta-analysis of controlled clinical trials by Bech and Cialdella (1992) which found those three symptoms in higher rates in patients on amitriptyline than those on citalopram. Again this may reflect a different side effect profile of doxepin from other tricyclic antidepressants. In addition, a possible reason for the high incidence of increased sweating is that perspiration did not diminish in frequency after the first few weeks of therapy, as suggested by Milne and Goa (1991). Other effects, light-headedness, increased sleep and anxiety/ agitation, were found less frequently in patients taking citalopram compared to trazodone. However, these three symptoms were reported more frequently in the citalopram group, compared with the doxepin group.

The number of respondents taking moclobemide was low, however some symptoms were common to other antidepressants. Dry mouth was reported with lower frequency by patients taking moclobemide than those taking other drugs, except citalopram, although it was still most frequent. However headache and nausea/ vomiting, symptoms frequently reported to the CSM, were also common. Other workers (Amrein et al., 1997; Stabl et al., 1989; Hilton et al., 1995; Fitton et al., 1992; Chen and Ruch, 1993) have compared moclobemide with tricyclic antidepressants and found headache, reduction in sleep, dry mouth and unusual tiredness to be higher in frequency with moclobemide. However, those workers found nausea and palpitations with a similar frequency in both groups and dizziness in lower frequency or at least comparable frequency in moclobemide group. Nightmares also reported by these workers could not be compared with other drugs in pilot study as it was not available in the pilot study questionnaires.

Many of the symptoms reported to nefazodone were cited in other studies (Drugdex Drug Evaluation Monographs, 1998; Robinson et al., 1996; Baldwin et al., 1996; Feiger et al., 1996; Augustin et al., 1997; Fontaine, 1993; Preskorn, 1995; Cyr and Brown, 1996). While many of the interval estimates compare well with the incidences from those studies, other symptoms namely paraesthesia, decrease in sexual desire, tremor and anxiety/ agitation were found in higher percentages in the present study.

Similarly, common side effects from citalopram, i.e. nausea/ vomiting, increased perspiration, headache, dry mouth, tremor, insomnia, sedation, dizziness and constipation (Milne and Goa, 1991) were among the top ten symptoms reported in this study. Also, the incidence estimates of dry mouth, unusual tiredness/ weakness, increased sweating and anxiety/ agitation in the present study were among those ranges identified (Drugdex Drug Evaluation Monograph, 1998; Milne and Goa, 1991;

Bech and Cialdella, 1992), while increased sleep, tremor, headache and decrease in sexual desire were found in higher proportions.

Interestingly more of the frequencies of reports from moclobemide treated patients were comparable to incidence estimates obtained from Drugdex Drug Evaluation Monographs (1998), Fitton et al. (1992), Amrein et al. (1997), Hilton et al. (1995), Chen and Ruch (1993), Stabl et al (1989), Larsen et al. (1984) and Moll et al. (1994), despite the relatively small sample size for moclobemide (16) in the present study.

The very low response rate for return of questionnaires to fentanyl patch (13%) was probably due to its use for severe pain, in particular cancer pain. Thus many patients were probably too ill to complete the questionnaires and a number of patients sent questionnaires had in fact already deceased (7 out of 64). Other research has shown that 9-17% of patients withdrew from clinical trials due to intolerable adverse effects from fentanyl patch (Calis et al.,1992; Sloan et al., 1998). The present study found that a high percentage of respondents using fentanyl patch perceived the most bothersome symptoms reported as severe (38%), which was greater than in those on tramadol (14%). This may suggest that fentanyl patch tended to produce more severe side effects than tramadol.

Almost all of the top ten symptoms reported and the most bothersome symptoms from fentanyl patch were established ADRs, with the exception of weight loss. The higher frequencies found with fentanyl patch for the common symptoms to fentanyl patch, tramadol and co-proxamol were probably due to the small number of respondents using fentanyl patch. However the incidence of bronchospasm was interesting, particularly when compared to CSM data and bearing in mind that many patients claimed to be suffering from abdominal pain. The potency of fentanyl patch may also

have been a factor in the increased frequency of symptoms, although with the exception of constipation and abdominal pain, estimated incidence rages were in line with those found in other studies (Drugdex Drug Evaluation Monograph, 1998; Sloan et al., 1998; Sandler, 1992; Grond et al., 1997; Calis et al., 1992; Miguel et al., 1995).

The classification of symptoms reported using the eight criteria for the three different therapeutic groups of drugs including pilot study showed that a lower percentage of probable ADRs were found for anticonvulsants, compared to antidepressants and analgesics. This may be an effect from higher proportions of respondents taking other drugs with the same indication in the anticonvulsant group (89%) than other groups (antidepressants 19%, analgesics 60%). Thus, it is less likely that symptoms would be classed as being caused only by the anticonvulsants. Fewer symptoms were classed as being caused by disease states in those reported to analgesics (31.6%) than to anticonvulsants (58.2%) and antidepressants (50.0%). This is probably because disease-related symptoms in patients with pain were very different from symptoms likely to be related to the study drugs. The higher overall proportion of symptoms reported from antidepressants which were potentially caused by study drugs suggests that the questionnaire may be particularly suitable for this class of drugs.

Chapter 8

Overall discussion and conclusion

8.1 Overall discussion

The questionnaire developed for this study comprised lists of symptoms in all body systems to enable the detection of a wide range of potential ADRs. Although the drugs studied were from only three therapeutic classes, the questionnaire was designed to be usable for any class of drug. It was hoped by this means to reduce bias and minimise false positive responses. The questionnaire was distributed directly to patients known to have been prescribed the drugs being studied, not via health professionals and relied solely on patient co-operation. The overall response rate for the pilot and main study together was approximately 40%. This is similar to a 39% response rate found in a study of patient self-reporting via forms distributed by community pharmacists in Australia (Mitchell et al., 1994). It is possible to obtain much higher response rates to questionnaires from patients if these are distributed by doctors, however there are major problems in ensuring adequate distribution (Stewart, 1999). While there were relatively few respondents for some drugs, such as fentanyl patch, moclobemide and topiramate, with the exception of fentanyl patch, this was due to the small number of questionnaires distributed. This was also the case in the pilot study. Data obtained from these questionnaires is therefore less representative of the population receiving these drugs. A large number of questionnaires were issued to most of the Grampian population who had been prescribed tramadol and venlafaxine over a three-month period. This resulted in a large number of questionnaires being returned from these patients (tramadol=344, venlafaxine=263), which enabled

comparison of the results with published information on the safety profiles of both drugs, since these were more likely to be representative.

There were a relatively high number of non-respondents, some of whom may have experienced adverse effects from the study drugs. It is possible that patients who did experience symptoms they felt to be drug-related would be more likely to return questionnaires. Based on this possibility, an assumption was made that non-respondents had no symptoms, to enable estimates of the lowest incidence of potential ADRs to be made. Using the number of respondents as a denominator resulted in estimates of highest incidence, therefore it was possible to obtain a range of incidence estimates, which could be compared to published studies. It was recognised that the results obtained are point prevalences and that method thus excludes any patients who may have had ADRs and either stopped the study drugs or switched to some other drugs before the questionnaires were distributed.

The method involved manual retrieval of patient names and addresses from the patients' prescriptions at the PPD in Aberdeen, which was very time-consuming. A surprisingly large number of prescriptions were in doctors own hand-writing of which some were illegible. This resulted in a number of questionnaires being returned unopened because of wrong addresses or wrong names, which contributed to the low response rates. In future, prescriptions will include CHI numbers, which would reduce the problems encountered in identifying patient details. However there are also ethical considerations in using prescription details to identify patients, which have been highlighted since the study was undertaken (Anonymous, 1999). In fact there were complaints from a small number of patients receiving the questionnaires respecting confidentiality. Additional information explaining how their details had been obtained was provided to all patients and the questionnaires stated that all information collected would be treated in the strictest confidence. However there were queries about these

points from some patients, who nonetheless returned questionnaires and also a few concerns expressed about the safety of the drugs they were taking. Anxiety generated by being invited to take part in research has been identified (Jones et al., 1995) and these workers suggested that an explanation of the data held by the researchers could overcome some problems. Reminder letters may undermine patients' confidence in the assurances given by researchers of confidentiality and the lack of effect of not participating on future care (Jones et al., 1995). The decision not to issue them on these grounds also affected the response rate. While there was an attempt to determine whether the questionnaires caused anxiety in the pre-pilot phase, only a small number of patients were interviewed. Although the questionnaires emphasised that all symptoms listed were not entirely the side effects from the study drug, misunderstanding may have remained about the drug safety which resulted in patients seeking advice from their doctors. In fact there was a study by De Wit et al. (1996) which demonstrated that 94% of respondents had no objection to the reporting of ADRs by their doctors or pharmacists and 77% did not object to the use of their medical data, even if these data were not anonymous, as long as the data were kept strictly confidential. Nonetheless it may have been preferable, in view of the potential for anxiety, to use alternative distribution methods.

The method relied on information supplied by patients, therefore the pilot study was designed to obtain access to all respondents' medical notes to check the accuracy of the data. Similarly, information from a sample of respondents receiving the two drugs for which most questionnaires were returned was also validated by accessing their medical records. While data was not inaccurate, details of concomitant drugs and disease states was frequently incomplete. This is a limitation of any study relying on patients as an information source. In the present study, it undoubtedly had an effect on the classification of symptoms in those whose notes were not examined.

The vast majority of the respondents (89%) reported at least one symptom and the symptoms covered a wide range. This is lower than that found by Ciccolunghi and Chaudri (1975) in a study of factors influencing the reporting of symptoms in which 97% of patients reported at least one symptom. The latter study used a 38-item checklist, which was shorter than the generic questionnaire used here. It had been found by Fisher et al. (1995) and Willison et al. (1995) that checklist questionnaires result in a higher frequency of reported symptoms than interview methods. This suggests that questionnaires may detect more drug-related symptoms, but may also result in reports of symptoms which are unattributable to the study drugs, as was found in the present study. Some of these unattributable symptoms could have been previously unrecognised ADRs to the newer drugs, although the similar frequency of unattributable symptoms to established drugs suggests otherwise. The method may also have caused patients to experience an increase in side effects due to suggestion from the symptoms listed in the questionnaires, especially mild symptoms as proposed by Borghi et al. (1984).

About two third of respondents in both the main and pilot study were female which may have been related to the high numbers receiving antidepressants. However a majority of females were also found in other patient self-monitoring studies by Fisher et al. (1993), Barber and Santanello (1995) and Mitchell et al. (1994). The finding that the response rates were however lower in patients taking antidepressants than in patients with neurological problems suggests that those with psychological problems were less willing to participate in the study.

Age was not related to the number of reported symptoms and there was no association between number of reported symptoms and number of concomitant drugs which is similar to the findings of Fisher et al. (1993) and Hallas et al. (1991). There was, however, an association between the number of symptoms reported and symptom

severity. In addition, patients who perceived most bothersome symptoms as severe were more likely to have informed their doctors about the symptoms reported in the questionnaires. These results provide evidence that self-reporting patients tend to report symptoms that were especially bothersome to them, as was also found by Fisher (1995). This is confirmed by the finding that patients often rated the severity of their symptoms more than merely minimally and moderately, which is in concordance with the studies by Fisher et al. (1993) and Buckingham et al. (1997). Many of the most frequently reported symptoms were also cited as the most bothersome symptoms.

Although over-reporting and inaccurate attribution will undoubtedly be a problem with such a system, the importance of patients' perceptions is increasingly being recognised (The Royal Pharmaceutical Society of Great Britain, 1997). Data from the medical records of over 300 patients found that only 22.4% (522/ 2330) of the symptoms patients claimed to experience were recorded by their GPs. While most of symptoms reported in the questionnaire were minor, they could have an effect on medicine-taking. In the majority of cases, when symptoms were recorded in medical notes, they were not described as drug side effects but as symptoms. It is of course probable that some were likely to be symptoms of existing disease states. However it is possible that doctors are not considering the possibility of adverse reactions when patients do report new symptoms. This could lead to further inappropriate prescribing to relieve the symptoms, but may also be a factor contributing to under-reporting. Interestingly, only seven reports were submitted from Grampian to the CSM relating to tramadol and sixteen to venlafaxine over the 14-month period which patients were reporting on.

Where numbers were sufficient to allow comparisons to be made with data from the CSM, it was found that many of the most frequently reported symptoms occurred with higher frequency in the present study. Symptoms reported by patients were also more

minor and known ADRs, while the Yellow Card method tended to detect more prominent and serious ADRs. This finding is comparable to studies by Mitchell et al. (1989, 1994) and van den Bemt et al. (1999) which concluded that patient-self reporting appeared to identify established ADRs particularly to new drugs, while reports from health professionals tended to report more rarer and more severe reactions. While it should be feasible to detect rare and serious reactions using patient questionnaires, larger sample sizes than that of the present study would be required. Other evidence suggests that the most frequently documented ADRs in clinical trials and other PMS studies were noted very infrequently in spontaneous reports (Cossmann et al., 1997). It is also known that the Yellow Card system suffers from under-reporting (D' Arcy, 1996; Speirs et al., 1994; Martin et al., 1998; Walker and Lumley, 1986). Therefore it is not surprising that the present study found greater percentages for many symptoms and detected different symptoms than data from the CSM. Higher frequencies for many symptoms were also found in the present study when data were compared with those from PEM studies. The latter method seemed to detect symptoms which occurred more frequently in the early stages of treatment, reflecting the fact that PEM studies are concerned with events during the first six months of therapy (Freemantle et al., 1997). Respondents in the present study had been taking the study drugs for longer periods, therefore symptoms which disappeared on continuing treatment or to which tolerance developed were less likely to be detected by this method, although patients were asked to report any suspected symptoms related to the study drugs in the 12 months previous to receiving the questionnaire.

Over-reporting and the need to use lay terminology for the questionnaire, which resulted in the need to adapt or combine terms from CSM data, could also have contributed to the differences found. Both the Yellow Card system and PEM studies rely on the willingness of health professionals to report symptoms, but are also dependent on patients reporting symptoms to them. It is perhaps not surprising that

symptoms such as decreased sexual desire were detected more frequently by the present method. The findings indicate that a large number of patients in the community actually suffer from minor and known ADRs. This supports the suggestion that an ADR monitoring system based on reports from patients would be inexpensive and might lead to faster identification of symptomatic reactions to some new drugs (Mitchell et al., 1988).

Although the numbers in the pilot study were small, some comparisons of the symptoms reported to different drugs within therapeutic classes were in line with other published data. For example, there were more frequent reports of drowsiness, nausea/ vomiting and dizziness to tramadol than to co-proxamol, the anticholinergic effect dry mouth was found more frequently with doxepin, a tricyclic antidepressant, than with the newer antidepressants venlafaxine and nefazodone. Insomnia was more prevalent with lamotrigine than carbamazepine and weight loss was more frequent with topiramate than carbamazepine and sodium valproate. However, other comparisons did not concord with existing data, for instance, the present study found that increased sweating occurred more often with venlafaxine than with trazodone, loss of memory, dizziness and reduction in sleep were reported in greater percentages in those taking lamotrigine than in those taking carbamazepine and dizziness was found in higher frequency with nefazodone than trazodone. These differences may be related to duration of therapy, small numbers in some cases or to the presence of concomitant drugs with similar side effect profiles. The vast majority of patients taking the anticonvulsants studied, for example, were also taking other anticonvulsants. Overall, patients taking other centrally acting drugs tended to report more symptoms. Given the method used, neither this nor other confounding factors such as other disease states, dosage regimen, duration of therapy and patient characteristics could be controlled.

The estimates of incidence range for many of the symptoms reported in the present study were comparable with incidences found in other published data which included both premarketing and postmarketing studies. These comparisons are possibly more useful than the CSM or PEM data, since pre-marketing studies and clinical trials involve systematic enquiries of all patients taking the drugs studied and consequently do not have the problem of under-reporting. Disappointingly, although the researchers contacted the manufacturers of tramadol and venlafaxine to request any data on file involving drug tolerability, only one published paper, which we already had, was provided for venlafaxine, and none for tramadol. Many of the frequently reported symptoms in this study were cited as common ADRs from published data. These findings may suggest that patient self-reporting appeared to be an effective method for detecting ADRs, especially for new drugs. However, for a number of symptoms, higher reporting rates were found in the present study. Duration of therapy may again be a factor contributing to these differences since there were a limited number of studies of long term therapy, while the majority of respondents in the present study (54%) had been taking the study drugs for more than six months. Over-reporting by some patients of symptoms associated with concomitant drugs or disease states and the small sample sizes for some study drugs are also likely to affect the comparability with published work.

The pre-pilot study showed that patients had difficulty in remembering start and stop dates of both study drugs and concomitant drugs. As a result, the questionnaire was modified to maximise response rates which could have been affected by inability to complete questions. This resulted in minimal data being available to enable symptom causality to be estimated and the consequent need for a classification system to be developed which did not require such detailed information as those in common use (Kramer et al., 1979; Naranjo et al., 1981; Venulet et al., 1986a, 1986b; Benechou and Danan, 1991). The system involved simple categories designed to enable

classification of symptoms reported into different probability levels of a causal relationship. It used information on known ADRs and symptoms of disease states, but did not require exact time relationships. Hence, none of symptoms reported in this study could be classified as definitely caused by the study drugs. The classification system was used by an independent expert (a pharmacist specialising in ADRs) to categorise 716 of the 5033 total symptoms reported. This provided an estimate of accuracy of the researcher classifications. There was agreement for 70-80% of reported symptoms (Kappa = 0.4-0.5). This is in line with that using conventional categories (Naranjo et al., 1981) and that using standardised assessment (Venulet et al., 1980). While there were 20-30% of symptoms over which there was disagreement, many studies have found similar disagreements, since these are subjective decisions based on experience and knowledge (Koch-Weser et al., 1977; Kramer et al., 1979; Meyboom et al., 1997; Venulet et al., 1980; Naranjo et al., 1981). Attempts to lessen disagreement by establishing various criteria to assess the causality of ADRs have not obviously improved level of agreement.

Using the eight criteria, which were developed into four categories of attribution, it was found that patients were likely to report symptoms which could have been attributed to the study drugs rather than those not attributed to the study drugs. This suggests that patients were reporting with a useful degree of accuracy, similar to that found by Fisher et al. (1994), Solovitz et al. (1987) and Mellinger et al. (1988). However, only 12% and 16% of symptoms reported in the pilot study and main study, respectively, were known to have been previously reported to the study drugs and no other obvious causes among concomitant drugs or diseases and could therefore be classed as probable ADRs. This illustrates the difficulties associated with patients' self-reporting, since it becomes impossible to attribute symptoms to particular drugs without details of time relationships. Again, it must emphasised that in most cases, the only information on concurrent drugs and disease states was obtained from patients, thus was often

incomplete or may also be unreliable. The majority of symptoms fell into the category of possible ADR, since they could also have been caused by concomitant drugs and/ or diseases. In addition, some patients also seemed to report symptoms which bothered them a lot even though they were unlikely to be caused by the study drugs, such as patients taking tramadol who reported bone and joint pain. Mitchell et al. (1988) also found that many of the events reported by patients taking amoxycillin or co-trimoxazole were related to their illness. It is difficult for patients to judge which symptoms were caused by the drugs with any degree of certainty. The disagreement over some classifications found here and in other studies suggest health professionals also have difficulty. Several studies have found that one of the main reasons for doctors not reporting an ADR was uncertainty about whether the reaction was caused by the suspected drugs (Scott et al., 1987; Bateman et al., 1992; Inman and Weber, 1986; Smith, 1987). A surprisingly high number of symptoms reported (10% in pilot study and 12% in main study) could not be attributed to any of patients' drugs or disease states. This suggest that some patients may have over-reported, as was found in a study by Borghi et al. (1984). Patients who reported few symptoms were less likely to report both unattributable symptoms and unlikely ADRs.

There are important limitations in the present study on patient self-reporting which should be noted. This study was performed retrospectively and relied mainly on information provided by patients, which could be incomplete and unreliable. Also data concerning dechallenge and rechallenge were unavailable. Other relevant information, such as exact time-relationships between the reactions and the drugs taken and laboratory data were also missing. Even though in some cases further information was obtained from medical records, some important data, such as start date and stop date of drugs taken were sometimes not recorded. This problem is a common one in general practice, as illustrated by the finding that only 23% of a total 155 sets of medical notes had a complete repeat medication record (Mansfield, 1986). The

method is unlikely to detect ADRs which need laboratory information or physiological measurements, such as blood disorders, cardiovascular, hepatic or renal dysfunction. Delayed ADRs, e.g. interstitial nephritis, cancer, are also unlikely to be detected by this method. Although patients also reported reasons for hospital admission after starting the study drugs, the method did not detect any serious ADRs which caused hospitalisation. It is not certain whether this is in fact feasible using the questionnaire, although large sample sizes would almost certainly be required. One postmarketing study in a very large number of patients taking antibacterial agents (15172) using questionnaires via a pharmacy-based approach found that only 13 patients were admitted to hospitals with 14 events which were possibly related to the target drugs and only one event was identified as due to the target antibacterial (Borden and Lee, 1982). Most patients tended to report symptoms they perceived as relatively severe possible ADRs, however some serious real ADRs may be unreported because patients may not have perceived them to be important or related to their drug, such as bruising or passing dark brown urine. The extent of under-reporting is unknown. On the other hand, a number of patients tended to over-report symptoms which were probably related to their disease states rather than the study drugs. They were also likely to report more symptoms which bothered them a lot or interfered with their lifestyle, but would be regarded as minor side effects, such as dry mouth, increased sweating, weight changes and reduction in sleeping. It is also possible that information about which ADRs to expect during treatment provided on patient information leaflets by community pharmacists could have improved the quality of their reporting.

Unlike controlled clinical trials, the total number of patients on each study drug was not available to provide an appropriate comparison and the number of patients who had stopped the study drugs because of adverse effects, particularly at the beginning of therapy, may have been underestimated by the method used. The actual number of patients were not provided from CSM and PEM, therefore, the data had to be adapted

to enable comparisons using similar denominators. This lead to the loss of some data and may also have contributed to bias in the comparisons, since there were many more reported symptoms per patient than those per CSM report. The inability of the method to identify definite ADRs and to use standard classification systems for causality is also a drawback.

Nonetheless, as no single method is without limitations, the present study suggests that this patient self-reporting questionnaire would be a valuable addition to systems for screening ADRs associated with drug use in the community. It is suggested that the method could provide meaningful information which is complementary to that obtained using other PMS methods. While it is expensive to follow cohorts of patients, especially considering the large sample sizes required to detect ADRs with low incidence, patient self-reporting is an extremely cost-effective method. The method can obtain early patient reports about possible ADRs of newly marketed drugs and is particularly useful for monitoring CNS drugs which necessarily require information from patients about behavioral and subjective symptoms. Such a method may also help the early identification of ADRs which could be further investigated using the other existing PMS methods including voluntary reports from health professionals or pharmaco-epidemiological studies. It is likely that this method based on patient self-reporting might also have a capacity to generate early signals of previously unknown symptomatic reactions with new drugs, if sample sizes are adequate as was found by Coulter (1988) for eye pain associated with nifedipine. Furthermore, the present study suggests that the interpretation of patient self-reports by pharmacists which could be followed where necessary by interview could assist in increasing ADR reporting rates. This could be particularly useful for newer drugs. There is considerable evidence to suggest that both hospital and community pharmacists in the UK have a potential role in detecting and monitoring ADRs and could increase the ADR reporting rates (Booth et al., 1988; Bussy et al., 1985; Edwards et al., 1989; Lee et al., 1997, 1993; Veitch

and Talbot 1985; Khan and Archer, 1994; Davis et al., 1999; Whittlesea and Walker 1996a, 1996b; Wolfson et al., 1993). Their contribution in the area of ADR reporting has also been accepted or encouraged by doctors, the CSM, the Royal Pharmaceutical Society of Great Britain, Family Health Services Authorities as well as the Royal College of General Practitioners (Sheppard et al., 1995; Nuffield Foundation, 1986; The Royal Pharmaceutical Society of Great Britain, 1992; Sutters and Nathan, 1993a, 1993b). The use of a questionnaire such as the one developed for this study could be valuable in enabling pharmacists, in particular those in the community, to extend their involvement in patient care to ADR monitoring and reporting. Pharmacists are uniquely placed to influence medication use at both prescriber and patient levels and their role in minimising ADRs occurring in the community is likely to increase in the future.

Pharmacists are increasingly working in medical practices (Weir et al., 1997; Martin et al., 1998) and undertaking medication reviews. It would be useful to evaluate the patient self-completion questionnaire and the pharmacists' screening of it in this situation, perhaps prior to interview. Another option could be to develop a short form of the postal questionnaire for patients arriving at the surgery for appointments or to collect repeat prescriptions to complete, which pharmacists could screen for problems which should be reported to the patient's GP. Here again pharmacists could subsequently be involved in taking more extensive drug histories as appropriate and in completing ADR reporting forms, enabling suitable cases to be submitted to the CSM with GP approval. Alternatively, the questionnaires could be distributed to patients who present their prescriptions for a particular drug class via community pharmacists. Patients could be encouraged to report any adverse reaction by some kind of incentive, such as gift vouchers, prize draws, while the questionnaires could be returned to a central point in pre-paid envelopes provided as in the present study. Further research into the use of open-ended questionnaires, such as that developed

for the pilot study would be useful, as it may identify any bias caused by suggestion through the checklist questionnaires. In addition, research is needed into the use of the checklist questionnaire in the present study for other drug classes which have fewer known ADR, differing from those in the present study, such as drugs for treating gastrointestinal disorders, antibiotics, NSAIDs. This could also help in validating the questionnaire and estimating the accuracy of patients' attribution of reported symptoms. Studying drugs with fewer adverse effects and diseases with fewer symptoms may result in increased chances of reporting known ADRs using checklist questionnaires. Further work is also needed into methods of enhancing the reliability of information provided by patients. Studies would ideally involve accessing all medical records or patient interview in a sample. The comparisons of patients' judgement of symptoms related to drugs with those of an expert panel would also be interesting. Applying the same type of questionnaire to healthy subjects who have not received any drug would also be valuable to identify the frequency of any general background symptoms. In order to obtain more representative results, further studies should recruit a high number of patients, in particular new drugs. This would improve the reliability of the data obtained enabling better comparisons. Multi-centre or nation-wide studies would be required for this.

8.2 Overall conclusion

The study demonstrated the feasibility of obtaining symptom reports from patients using a novel checklist, which were mainly classed as possible or probable ADRs. The symptoms reported were mostly known side effects to the drugs studied, although reported with higher frequency than in CSM or PEM data. Although serious and novel ADRs are less likely to be detected using this method, it shows that ADRs are common in the community. The data is of value, since patient involvement in treatment decisions is increasingly recognised as important. The questionnaire has a number of potential applications which should be further investigated.

Glossary

Adverse drug events (ADE) - any unfavourable occurrence that occurs during or following clinical use of a drug, but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction (ADR) - any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy. Alternatively, ADR is an adverse drug event which is judged to be caused by the drug.

Adverse Drug Reactions On-line Information Tracking (ADROIT) - a computer database which holds ADR reports submitted to the CSM in the UK by combining images processing with a relational data base, organised by the MCA.

Causality assessment - an assessment of the likelihood in an individual case that the suspected drug caused the adverse reaction.

Committee on Safety of Medicines (CSM) - a committee which has specific responsibilities for promoting the collection and investigation of information related to adverse drug reactions in the UK.

Community Health Index (CHI) - a unique patient identifier which is issued to individual patients in Scotland when they register with general practitioners.

Drug monitoring - any procedure which aims at providing systematic inferences on likely chains of causation linking drugs and adverse reactions within a population.

Ethical Committee - an independent body who considers clinical research studies in the context of safety, integrity and human rights.

Incidence rate of a reaction - a measure of a how frequently the reaction occurs. Specifically, it is the number of new cases of the reaction which develop over a defined time period in a defined population at risk, divided by the number of the people in that population at risk.

Medicines Control Agency (MCA) - an organisation which is responsible for licencing of medicines in the UK, monitoring the safety, investigating possible hazards and taking action to minimise the risks to users.

Pharmacoepidemiology - the study of drug use and its effects, both beneficial and adverse, in large populations.

Pharmacy Practice Division (PPD) - an organisation of the Common Services Agency which is responsible for a number of activities including examination, checking, investigation and pricing of prescriptions for drugs, medicines and listed appliances supplied as pharmaceutical services under the National Health Service in Scotland.

Postmarketing surveillance (PMS) - the study of drug use and drug effects after marketing.

Prescription- Event Monitoring (PEM) - a system of postmarketing surveillance established by the Drug Safety Research Unit at Southampton University which aims to monitor all drugs used in general practice in England.

Prevalence rate of a reaction - a measurement of how common the reaction is. Specifically, it is the number of existing cases of the reaction in a defined population at a given point in time, divided by the number of people in that population.

Prospective studies - studies performed simultaneously with the events under study.

Retrospective studies - studies conducted after the events under study.

Side effect - any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological properties of the drug.

Spontaneous reporting system (SRS) - a postmarketing surveillance method which is dependent on voluntary collaboration by doctors and other health professionals submitting ADR reports to drug regulatory authorities at the national level.

Type A adverse reaction - a reaction which is the result of an exaggerated but otherwise predictable pharmacological effect of a drug. They tend to be common, dose-related, and less serious than Type B reactions.

Type B adverse reaction - a reaction which is an aberrant effect of the drug. They tend to be uncommon, not dose-related, and unpredictable.

Yellow Card Scheme - the spontaneous reporting system in the UK which is organised by the CSM.

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Appendix A: Joint Ethical Commmitee approval

GHB Grampian Health Board

GRAMPIAN HEALTH BOARD
AND
UNIVERSITY OF ABERDEEN

JOINT ETHICAL COMMITTEE

Chairman:

Professor C Kidd
School of Biomedical Sciences (Physiology)
Marischal College
Broad Street
ABERDEEN

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Clerk to the Committee:

Ms Lynn Conway
Dept of Public Health Medicine
Grampian Health Board
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2 Eday Road
Aberdeen, AB15 6RE

Tel: (0224) 663456 Ext.75225
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Our Ref: LC\IAA

Project No:96\179

30 July 1996

Dr N Jarernsiripornkul
PhD Student
School of Pharmacy
The Robert Gordon University
Schoolhill
Aberdeen

Dear Dr Jarernsiripornkul

Pharmacist input into patients' self-reporting of adverse drug reactions

The above project was considered at the Joint Ethical Committee meeting of 25th July 1996, and I am pleased to confirm that ethical approval for this project has now been granted, subject to two minor amendments to the patient information sheet: (I) in paragraph one change "your doctor has given me permission" to "your doctor is aware of this study", and (ii) remove "But, it would be great if you could help me".

With regards to medical indemnity, I enclose a form which should be completed and returned to either: (i) Dr J Hern, Clinical Director, Aberdeen Royal Hospitals NHS Trust, Foresterhill House, Ashgrove Road West, Aberdeen, (ii) Dr R Scorgie, Medical Director, Grampian Healthcare NHS Trust, Westholme, Woodend Hospital, Aberdeen, or (iii) Clinical Director, Moray Health Services NHS Trust, 317 High Street, Elgin, as appropriate, if you wish one of the above Trusts to accept liability for medical indemnity for this project. Where drugs are received from a drug company for use in a trial, these must be stored in the Pharmacy Department for reasons of good practice.

We would be very glad to receive, in due course, copies of any publications arising from this research. Thank you for bringing this study to the Committee's attention.

Yours sincerely,

Lynn Conway

Lynn Conway,
Clerk to the Committee

.....
.....

Please quote project number in all correspondence

Appendix B: Pre-pilot questionnaires

2 September 1996

Dear

We are writing to ask for your help with a study we are carrying out about side effects from medicines. At the moment we are trying to find a questionnaire that patients will be able to fill in, to tell us about any experiences they have had since taking their medicines.

We have enclosed a questionnaire which we would like you to fill in. We will then contact you to arrange a visit so that you can tell us how easy or difficult you found it. This will help us to choose the best type of questions to use for other patients to fill in.

We hope you will be able to help us with this study. Please do not worry if you find any questions difficult. We want to find out what you think about our questionnaire. One of us will contact you in the next week to arrange a time to come and see you about this study.

With many thanks

Yours sincerely

Dr P R S Duffus and Dr Janet Krska (Practice Pharmacist)

CONFIDENTIAL

Please tick (✓) and fill in where appropriate

PART 1 : GENERAL INFORMATION ABOUT YOU AND YOUR MEDICINE

1. Your Name: _____

2: Sex: 1 ☐ Male 2 ☐ Female

3. Age: _____ years old

4. When did you start taking your _____ ? (__ __ / __ __)
(Please try to fill this in, because it is important that we know this) month / year

5. What condition did your doctor prescribe this medicine for? _____

6. How many times a day are/were you taking this medicine?

1 ☐ Once a day
2 ☐ Twice a day
3 ☐ Three times a day
4 ☐ Four times a day
5 ☐ Other (please indicate) _____

7. How many tablets are/were you taking each time?

1 ☐ One
2 ☐ Two
3 ☐ Three
4 ☐ Four
5 ☐ Other (please indicate) _____

8. Please list all other medicines that you have taken regularly since starting_____and approximately when you started and stopped taking each. Please leave "Stop Date" blank for any medicines you are still taking. Again it is important that you try to remember.

Name of Medicine	Start Date (month/year)	Stop Date (month/year)
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

9. Do you have any other medical conditions?

1 ☐ Yes 2 ☐ No

If yes, please list them _____

_____

10. Since you started taking_____ , have you been in hospital for any reason?

1 ☐ Yes 2 ☐ No

If yes, what was the reason? _____

_____

PART 2 : EXPERIENCES OF POSSIBLE SIDE EFFECTS

Please try to complete all of this part, even though you may feel questions are repeated. This is to help us find out which way of asking the questions you find easiest.

Part 2A

Since starting_____ , have you had any symptoms? Please only describe symptoms which were not present before.

11. Do you have any symptoms/complaints related to your skin, hair or nails?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

12. Do you have any symptoms/complaints related to your muscles, bones or joints?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

13. Do you have any symptoms/complaints related to your head?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

Remember, only describe symptoms you have had since starting_____

14. Do you have any symptoms/complaints related to your eyes or vision?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

15. Do you have any symptoms/complaints related to your ears or hearing ?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

16. Do you have any symptoms/complaints related to your mouth, gums , nose, throat, neck or voice ?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

17. Do you have any symptoms/complaints related to your breathing or lungs?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

18. Do you have any of the following symptoms/complaints related to your heart or circulation?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

19. Do you have any symptoms/complaints related to your stomach or bowel movements?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

Remember, only describe symptoms you have had since starting_____

20. Do you have any symptoms/complaints related to your kidneys, bladder or urinary system?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

21. Do you have any symptoms/complaints related to your sexual function (ability) or your sex organ ?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

22. Do you have any symptoms/complaints related to your body movement or balance?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

23. Do you have any symptoms/complaints related to your mental health?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

24. Do you have any other symptoms/complaints that you have not described in the above questions?

1 ☐ Yes 2 ☐ No

If yes, please describe _____

_____

Part 2B

Since starting_____ , have you had any of the following symptoms? Please tick (✓) all the boxes which apply ,and only indicate the problems which were not present before.

25. Do you have any of the following symptoms/complaints related to your skin?

1 ☐ bleeding
2 ☐ bruising
3 ☐ burning sensation
4 ☐ flushing of skin
5 ☐ increased sensitivity of skin to light
6 ☐ itching of skin
7 ☐ pale skin
8 ☐ puffy skin
9 ☐ pins and needles sensation
10 ☐ skin rash
11 ☐ yellowing of skin
12 ☐ Other (please indicate) _____
13 ☐ None

26. Do you have any of the following symptoms/complaints related to your hair or nails?

1 ☐ change in fingernails
2 ☐ hair loss
3 ☐ Other (please indicate) _____
4 ☐ None

27. Do you have any of the following symptoms/complaints related to your muscles, bones or joints?

1 ☐ bone or joint pain
2 ☐ muscle pain or weakness
3 ☐ trembling & shaking of fingers & hands
4 ☐ unsteadiness on feet
5 ☐ unusual or uncontrolled body movement
6 ☐ Other (please indicate) _____
7 ☐ None

28. Do you have any of the following symptoms/complaints related to your head?

1 ☐ headache
2 ☐ migraine headache
3 ☐ Other (please indicate) _____
4 ☐ None

29. Do you have any of the following symptoms/complaints related to your vision?

1 ☐ reduced vision
2 ☐ double vision
3 ☐ Other (please indicate) _____
4 ☐ None

Remember, only tick the boxes that represent symptoms you have had since starting_____

30. Do you have any of the following symptoms/complaints related to your eyes?

1 ☐ itchy or irritated or inflamed eyes or eyelids
2 ☐ inability to move eyes
3 ☐ unusual movement of the eyes
4 ☐ Other (please indicate) _____
5 ☐ None

31. Do you have any of the following symptoms/complaints related to your hearing or ears?

1 ☐ change or difficulty in hearing
2 ☐ feeling of fullness in the ears
3 ☐ ringing, buzzing or noises in ears
4 ☐ Other (please indicate) _____
5 ☐ None

32. Do you have any of the following symptoms/complaints related to your mouth or gums ?

1 ☐ bleeding from gums
2 ☐ dry mouth or throat
3 ☐ Other (please indicate) _____
4 ☐ None

33. Do you have any of the following symptoms/complaints related to your nose, throat, neck or voice?

1 ☐ difficulty talking
2 ☐ slurred speech
3 ☐ runny or stuffy nose
4 ☐ sore throat
5 ☐ Other (please indicate) _____
6 ☐ None

34. Do you have any of the following symptoms/complaints related to your breathing or lungs?

1 ☐ cough
2 ☐ difficulty breathing
3 ☐ fast breathing
4 ☐ slow breathing
5 ☐ Other (please indicate) _____
6 ☐ None

35. Do you have any of the following symptoms/complaints related to your heart or circulation?

1 ☐ palpitations/ racing heart
2 ☐ missed heart beat
3 ☐ Other (please indicate) _____
4 ☐ None

Remember, only tick the boxes that represent symptoms you have had since starting_____

36. Do you have any of the following symptoms/complaints related to your stomach or digestive system?

1 ☐ bloated feeling or gas
2 ☐ decrease in appetite
3 ☐ indigestion
4 ☐ increase in appetite
5 ☐ stomach pain or cramps
6 ☐ vomiting
7 ☐ vomiting blood or material that looks like coffee grounds
9 ☐ Other (please indicate)
_____
10 ☐ None

37. Do you have any of the following symptoms/complaints related to your rectum or bowel movements?

1 ☐ black tarry stool
2 ☐ constipation
3 ☐ diarrhoea
4 ☐ Other (please indicate)
_____
5 ☐ None

38. Do you have any of the following symptoms/complaints related to your kidneys, bladder or urinary system?

1 ☐ burning, discomfort or pain while passing water
2 ☐ dark brown urine
3 ☐ difficulty in passing water
4 ☐ passing water less often
5 ☐ passing water more often
6 ☐ bloody urine
7 ☐ Other (please indicate)
_____
8 ☐ None

39. Do you have any of the following symptoms/complaints related to your sexual function (ability)?

1 ☐ decrease in sexual desire
2 ☐ decrease in sexual ability
3 ☐ increase in sexual desire
4 ☐ Other (please indicate)
_____
5 ☐ None

40. Do you have any of the following symptoms/complaints related to your reproductive (sex) organ?

1 ☐ abnormal or change in vaginal bleeding
2 ☐ burning or irritated penis
3 ☐ Other (please indicate)
_____
4 ☐ None

Remember, only tick the boxes that represent symptoms you have had since starting_____

41. Do you have any of the following symptoms/complaints related to your nervous system?

1 ☐ confusion or delirium
2 ☐ light-headed when getting up from a lying or sitting position or feeling faint
3 ☐ dizziness or staggering (vertigo)
4 ☐ increase in convulsions (seizures)
5 ☐ Other (please indicate) _____
6 ☐ None

42. Do you have any of the following symptoms/complaints related to your mental health?

1 ☐ anxiety (nervousness) or agitation
2 ☐ change in mood
3 ☐ difficulty concentrating or learning
4 ☐ hallucinations (seeing, hearing or feeling things that are not there)
5 ☐ anger
6 ☐ loss of memory
7 ☐ thought of suicide
8 ☐ reduction in sleeping
9 ☐ increase sleep or drowsiness
10 ☐ Other (please indicate) _____
11 ☐ None

43. Do you have any of the following symptoms/complaints?

1 ☐ increased sensitivity to cold
2 ☐ excessive thirst
3 ☐ fever
4 ☐ flu-like symptoms
5 ☐ hot flushes
6 ☐ increase sweating
7 ☐ unusual tiredness or weakness
8 ☐ weight gain
9 ☐ weight loss
10 ☐ Other (please indicate) _____
11 ☐ None

44. Which of the symptoms have bothered you most ?

_____

and how much has it (have they) bothered you at worst ?

1 ☐ minimally
2 ☐ mildly
3 ☐ moderately
4 ☐ severely
5 ☐ very severely

45. Do you think any of the above symptom(s) you have described may possibly be caused by _____ ?

1 ☐ Yes 2 ☐ No 3 ☐ Don't know

46. Have you told your doctor about this/these symptom(s)?

1 ☐ Yes 2 ☐ No

PART 3 :Only complete this section if you have stopped taking _____.

47. When did you stop this medicine? (__ __ / __ __)
month / year

48. Why did you stop?

1 ☐ I felt I didn't need it any longer
2 ☐ The doctor said I didn't need it any longer
3 ☐ The doctor told me to stop because I was having problems with it
4 ☐ I decided to stop because I was having problems with it
5 ☐ I felt it wasn't helping me
6 ☐ Other (please explain) _____

_____

49. Have any of the symptoms you have described gone away?

1 ☐ Yes 2 ☐ No

If yes, please say which ones.

_____

_____

50. Have any other symptoms started after stopping _____?

1 ☐ Yes 2 ☐ No

If yes, please describe them here.

_____

_____

Thank you for your time and co-operation.

Appendix C: Pilot questionnaire

FACULTY OF HEALTH AND FOOD

School of Pharmacy

Schoolhill
Aberdeen
AB10 1FR
United Kingdom
Tel: 01224 262000
Fax: 01224 626559

Reply to:

THE
ROBERT GORDON
UNIVERSITY
ABERDEEN

Dear Patient

I am writing to patients in Grampian who have been prescribed certain medicines. You have been prescribed one of these medicines and we are interested to know about your experiences since you have been taking it. Your name has been obtained from your prescription, but your doctor is aware of this study.

All medicines can still occasionally cause side effects. This study is going to be looking mainly at side effects of these medicines. To do this I would like you to fill in this questionnaire. It should take about 10-15 minutes for you to complete.

The questionnaire will ask you questions about:

1) general information about yourself
2) the medicines you take
3) any symptoms you feel after taking your medicine
4) whether you have told your doctor about any symptoms you have had.

This information will help us identify side effects which may be related to your medicine. This will then be of benefit to all patients who are prescribed this medicine.

Once you have completed the questionnaire, please send it back to me in the enclosed pre-paid envelope, if possible within 2 weeks.

Please don't worry.

All information collected will be treated in the strictest confidence. There is no need for you to take part in the study if you don't want to. You can pull out at any time and there will be no effect on your future medical care.

I would like to thank you for taking the time to fill in the questionnaire.

Janet Krska

Dr Janet Krska
School of Pharmacy
The Robert Gordon University

CONFIDENTIAL

Please answer all the questions in parts 1 and 2 by ticking or filling in where appropriate

PART 1 : GENERAL INFORMATION ABOUT YOU AND YOUR MEDICINE

1. Your Name: _____

2: Sex: 1 ❑ Male 2 ❑ Female

3. Age: _____ years old

4. How many times a day are/were you taking **Doxepin (Sinequen ®)** ?

1 ❑ Once a day
2 ❑ Twice a day
3 ❑ Three times a day
4 ❑ Four times a day
5 ❑ Other (please indicate) _____

5. How many tablets are/were you taking each time?

1 ❑ One
2 ❑ Two
3 ❑ Three
4 ❑ Four
5 ❑ Other (please indicate) _____

6. When did you start taking your **Doxepin (Sinequen ®)** ? (__ __ / __ __)
(Please try to fill this in, because it is important that we know this) month / year

7. What condition did your doctor prescribe this medicine for? _____

8. Please list all other medicines that you have taken regularly since starting **Doxepin (Sinequen ®)**. For each medicine please tick whether you started taking it before or after **Doxepin (Sinequen ®)**. Please also tick whether you have now stopped taking any of these medicines. **Again it is important that you try to remember.**

Name of Medicine	Started ?	Stopped ?
_____	❑ Before ❑ After	❑ Yes ❑ No
_____	❑ Before ❑ After	❑ Yes ❑ No
_____	❑ Before ❑ After	❑ Yes ❑ No
_____	❑ Before ❑ After	❑ Yes ❑ No
_____	❑ Before ❑ After	❑ Yes ❑ No

9. Do you have any other medical conditions?

1 ❑ Yes 2 ❑ No

If yes, please list them _____

_____

10. Since you started taking **Doxepin (Sinequen ®)**, have you been in hospital for any reason?

1 ❑ Yes 2 ❑ No

If yes, what was the reason? _____

_____

PART 2 : EXPERIENCES OF POSSIBLE SIDE EFFECTS

The purpose of this questionnaire is to find out whether you have experienced any side effects while taking your medicine. **Please be assured this does not mean your medicine can cause all of the effects listed here**. *If you are no longer taking your medicine, we would still like you to complete the questionnaire.*

During the last 12 months , have you had any of the following symptoms which you think may be side effects caused by Doxepin (Sinequen ®) ? Please tick all the boxes which apply and only indicate the problems which were not present before.

11. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your skin?

1 ❑ bleeding
2 ❑ bruising
3 ❑ burning sensation
4 ❑ flushing of skin/ hot flush
5 ❑ increased sensitivity of skin to light
6 ❑ itching of skin
7 ❑ pale skin
8 ❑ puffy skin
9 ❑ pins and needles sensation
10 ❑ skin rash
11 ❑ yellowing of skin
12 ❑ Other (please indicate) _____
13 ❑ None

12. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your hair or nails?

1 ❑ change in fingernails
2 ❑ hair loss
3 ❑ Other (please indicate) _____
4 ❑ None

Remember, only tick the boxes that represent symptoms you have had since starting Doxepin (Sinequen ®) .

13. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your muscles, bones or joints?

1 ❑ bone or joint pain
2 ❑ muscle pain
3 ❑ muscle weakness
4 ❑ trembling & shaking of fingers & hands
5 ❑ unsteadiness on feet
6 ❑ unusual or uncontrolled body movement
7 ❑ Other (please indicate) _____
8 ❑ None

14. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your head?

1 ❑ headache
2 ❑ migraine headache
3 ❑ Other (please indicate) _____
4 ❑ None

15. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your vision?

1 ❑ reduced vision
2 ❑ double vision
3 ❑ Other (please indicate) _____
4 ❑ None

16. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your eyes?

1 ❑ itchy or irritated or inflamed eyes or eyelids
2 ❑ inability to move eyes
3 ❑ unusual movement of the eyes
4 ❑ Other (please indicate) _____
5 ❑ None

17. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your hearing or ears?

1 ❑ change or difficulty in hearing
2 ❑ feeling of fullness in the ears
3 ❑ ringing, buzzing or noises in ears
4 ❑ Other (please indicate) _____
5 ❑ None

Remember, only tick the boxes that represent symptoms you have had since starting Doxepin (Sinequen ®) .

18. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your mouth or gums ?

1 ❑ bleeding from gums
2 ❑ dry mouth or throat
3 ❑ Other (please indicate) _____
4 ❑ None

19. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your nose, throat, neck or voice?

1 ❑ difficulty talking
2 ❑ slurred speech
3 ❑ runny or stuffy nose
4 ❑ sore throat
5 ❑ Other (please indicate) _____
6 ❑ None

20. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your breathing or lungs?

1 ❑ cough
2 ❑ difficulty breathing
3 ❑ fast breathing
4 ❑ slow breathing
5 ❑ Other (please indicate) _____
6 ❑ None

21. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your heart or circulation?

1 ❑ palpitations/ racing heart
2 ❑ missed heart beat
3 ❑ Other (please indicate) _____
4 ❑ None

22. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your stomach or digestive system?

1 ❑ bloated feeling or gas
2 ❑ decrease in appetite
3 ❑ indigestion or heartburn
4 ❑ increase in appetite
5 ❑ pain or cramps in lower abdomen
6 ❑ vomiting
7 ❑ vomiting blood or material that looks like coffee grounds
8 ❑ Other (please indicate) _____
9 ❑ None

Remember, only tick the boxes that represent symptoms you have had since starting Doxepin (Sinequen ®) .

23. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your rectum or bowel movements?

1 ❑ black tarry stool
2 ❑ constipation
3 ❑ diarrhoea
4 ❑ Other (please indicate) _____
5 ❑ None

24. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your kidneys, bladder or urinary system?

1 ❑ burning, discomfort or pain while passing water
2 ❑ dark brown urine
3 ❑ difficulty in passing water
4 ❑ passing water less often
5 ❑ passing water more often
6 ❑ bloody urine
7 ❑ Other (please indicate) _____
8 ❑ None

25. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your sexual function (ability)?

1 ❑ decrease in sexual desire
2 ❑ decrease in sexual ability
3 ❑ increase in sexual desire
4 ❑ Other (please indicate) _____
5 ❑ None

26. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your reproductive (sex) organ?

1 ❑ abnormal or change in vaginal bleeding
2 ❑ burning or irritated penis
3 ❑ Other (please indicate) _____
4 ❑ None

27. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your nervous system?

1 ❑ confusion or delirium
2 ❑ light-headed when getting up from a lying or sitting position or feeling faint
3 ❑ dizziness or staggering (vertigo)
4 ❑ increase in convulsions (seizures)
5 ❑ Other (please indicate) _____
6 ❑ None

Remember, only tick the boxes that represent symptoms you have had since starting Doxepin (Sinequen ®) .

28. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your mental health?

1 ❑ anxiety (nervousness) or agitation
2 ❑ change in mood
3 ❑ difficulty concentrating or learning
4 ❑ hallucinations (seeing, hearing or feeling things that are not there)
5 ❑ anger
6 ❑ loss of memory
7 ❑ thought of suicide
8 ❑ reduction in sleeping
9 ❑ increase sleep or drowsiness
10 ❑ Other (please indicate) _____
11 ❑ None

29. Have you had any of the following symptoms which you think may be due to side effects from this medicine?

1 ❑ increased sensitivity to cold
2 ❑ excessive thirst
3 ❑ fever
4 ❑ flu-like symptoms
5 ❑ increase sweating
6 ❑ unusual tiredness or weakness
7 ❑ weight gain
8 ❑ weight loss
9 ❑ Other (please indicate) _____
10 ❑ None

30. Which, if any, of the symptoms in question 11 - 29 have bothered you most ?

_____

31. How much has this symptom(s) in question 30 bothered you at its worst ?

1 ❑ minimally
2 ❑ mildly
3 ❑ moderately
4 ❑ severely
5 ❑ very severely
6 ❑ does not apply

32. Have you told your doctor about any of these symptom(s)?

1 ❑ All
2 ❑ Some
3 ❑ None
4 ❑ I'm not sure

Please ensure you have answered all questions in parts 1 and 2.

If you have stopped taking your medicine, please answer the questions overleaf.

Please return the completed questionnaire in the pre-paid envelope provided.

PART 3 : ONLY COMPLETE THIS SECTION IF YOU HAVE STOPPED TAKING Doxepin (Sinequen ®) .

33. When did you stop this medicine? (__ __ / __ __)
month / year

34. Why did you stop?

1 ❑ I felt I didn't need it any longer
2 ❑ The doctor said I didn't need it any longer
3 ❑ The doctor told me to stop because I was having problems with it
4 ❑ I decided to stop because I was having problems with it
5 ❑ I felt it wasn't helping me
6 ❑ Other (please explain) _____

_____

35. Have any of the symptoms you have described gone away?

1 ❑ Yes 2 ❑ No 3 ❑ Does not apply

If yes, please say which ones.

_____

_____

36. Have any other symptoms started after stopping **Doxepin (Sinequen ®)** ?

1 ❑ Yes 2 ❑ No

If yes, please describe them here.

_____

_____

Thank you for your time and co-operation.

Please return the completed questionnaire in the pre-paid envelope provided.

Number _____

Appendix D: Reminder letter to patients in pilot study

13th March 1997

Dear

A few weeks ago in February, I sent you a questionnaire asking about any side effects related to your medicine. So far, I have not received it yet. In case you have lost it, I am sending you another copy of the questionnaire which is enclosed. I would be most grateful if you return it in the enclosed pre-paid envelope no later than 27th March 1997.

I am working with doctors in a few practices, including Denburn Health Centre and Albyn Medical Practice , to study side effects of certain medicines. This information from you will help pharmacists and doctors everywhere to identify side effects which may be related to the medicine you are taking. This will then be of benefit to all patients who are prescribed this medicine.

Thank you very much in anticipation of your help.

Yours sincerely

Dr Janet Krska
School of Pharmacy
The Robert Gordon University

Appendix E: Data collection form from medical notes

Date..... GP ..... Questionnaire No.....
Last name ..... First name ..... Age ..... Sex .....
Dose ..... Start date in Q : ..... in C :.....

	Questionnaire	Case note (add)
concomitant drugs		
other diseases		

Side effects

Questionnaire	Date	Case note as	
		Symptom	Side effect

Informed doctor in Q : ..... in C : .....

Stop this medicine __ yes __ No
Side effects which have gone away.....
.....

Note: .....
.....
.....
.....
.....
.....

Appendix F: Main study questionnaire

FACULTY OF HEALTH AND FOOD

School of Pharmacy

Schoolhill
Aberdeen
AB10 1FR
United Kingdom
Tel: 01224 262000
Fax: 01224 626559

Reply to:

THE
ROBERT GORDON
UNIVERSITY
ABERDEEN

Dear Patient

I am writing to patients in Grampian who have been prescribed recently introduced medicines. You have been prescribed one of these medicines and we are interested to know about your experiences since you have been taking it. Your name has been obtained from your prescription, but your general practitioner is aware of this study.

These new medicines are often safer than older medicines. However, they can still occasionally cause side effects.

The main purpose of this study is to see if you have experienced any side effects from your medicine. To do this we would like you to fill in this questionnaire. It should take about 10-15 minutes for you to complete.

The questionnaire will ask you questions about:

1) general information about yourself
2) the medicines you take
3) any symptoms you feel after taking your new medicine
4) whether you have told your doctor about any symptoms you have had.

If you are no longer taking the medicine, we would still like you to complete the questionnaire. This information will help us identify side effects which may be related to new medicines more quickly. This will then be of benefit to all patients who are prescribed these medicines.

Once you have completed the questionnaire, please send it back to me in the enclosed pre-paid envelope, **if possible within 2 weeks.**

Please be assured this does not mean your medicine can cause all of the side effects listed in the questionnaire.

All information collected will be treated in the strictest confidence. There is no need for you to take part in the study if you don't want to. You can pull out at any time and there will be no effect on your future medical care.

I would like to thank you for taking the time to fill in the questionnaire.

Janet Krska

Dr Janet Krska
School of Pharmacy

Head of School
Professor R M E Richards
BPharm PhD DSc DPharmSci FRPha
PhC(Thai) PhC(Zimb)

CONFIDENTIAL

Please answer all the questions in parts 1 and 2 by ticking or filling in where appropriate

PART 1 : GENERAL INFORMATION ABOUT YOU AND YOUR MEDICINE

1: Sex: 1 ❑ Male 2 ❑ Female

2. Age: _____ years old

3. How many times a day are/were you taking **Tramadol (Zydol®)** ?

1 ❑ Once a day
2 ❑ Twice a day
3 ❑ Three times a day
4 ❑ Four times a day
5 ❑ Other (please indicate) _____

4. How many tablets or capsules are/were you taking each time?

1 ❑ One
2 ❑ Two
3 ❑ Three
4 ❑ Four
5 ❑ Other (please indicate) _____

5. When did you start taking your **Tramadol (Zydol®)** ? (__ __ / __ __)
(Please try to fill this in, because it is important that we know this) month / year

6. What condition did your doctor prescribe this medicine for? _____

7. Please list all other medicines that you have taken regularly **during the last 12 months**. For each medicine please tick whether you started taking it before or after **Tramadol (Zydol®)** . Please also tick whether you have now stopped taking any of these medicines. **Again it is important that you try to remember.**

Name of Medicine	Started ?	Stopped ?
_____	❑ Before ❑ After	❑ Yes ❑ No
_____	❑ Before ❑ After	❑ Yes ❑ No
_____	❑ Before ❑ After	❑ Yes ❑ No
_____	❑ Before ❑ After	❑ Yes ❑ No
_____	❑ Before ❑ After	❑ Yes ❑ No

8. Do you have any other medical conditions?

1 ❑ Yes 2 ❑ No

If yes, please list them _____

_____

9. Since you started taking **Tramadol (Zydol®)** , have you been in hospital for any reason?

1 ❑ Yes 2 ❑ No

If yes, what was the reason? _____

_____

PART 2 : EXPERIENCES OF POSSIBLE SIDE EFFECTS

The purpose of this questionnaire is to find out whether you have experienced any side effects while taking your medicine. Please be assured this does not mean your medicine can cause all of the side effects listed here. *If you are no longer taking your medicine, we would still like you to complete the questionnaire.*

During the last 12 months , have you had any of the following symptoms which you think may be side effects caused by Tramadol (Zydol®) ? Please tick all the boxes which you think apply. Only indicate the problems which were not present before you started taking **Tramadol (Zydol®)** .

10. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your skin?

1 ❑ bleeding
2 ❑ bruising
3 ❑ burning sensation
4 ❑ flushing of skin/ hot flush
5 ❑ increased sensitivity of skin to light
6 ❑ itching of skin
7 ❑ pale skin
8 ❑ puffy skin
9 ❑ pins and needles sensation
10 ❑ skin rash
11 ❑ yellowing of skin
12 ❑ Other (please indicate)
_____
13 ❑ None

11. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your hair or nails?

1 ❑ change in fingernails
2 ❑ hair loss
3 ❑ Other (please indicate)
_____
4 ❑ None

During the last 12 months , have you had any of the following symptoms which you think may be side effects caused by Tramadol (Zydol®) ? Only indicate the problems which were not present before you started taking **Tramadol (Zydol®)** .

12. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your muscles, bones or joints?

1 ❑ bone or joint pain
2 ❑ muscle pain
3 ❑ muscle weakness
4 ❑ trembling & shaking of fingers & hands
5 ❑ unsteadiness on feet
6 ❑ unusual or uncontrolled body movement
7 ❑ Other (please indicate) _____
8 ❑ None

13. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your head?

1 ❑ headache
2 ❑ migraine headache
3 ❑ Other (please indicate) _____
4 ❑ None

14. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your vision?

1 ❑ blurred vision
2 ❑ double vision
3 ❑ Other (please indicate) _____
4 ❑ None

15. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your eyes?

1 ❑ itchy or irritated or inflamed eyes or eyelids
2 ❑ inability to move eyes
3 ❑ unusual movement of the eyes
4 ❑ Other (please indicate) _____
5 ❑ None

16. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your hearing or ears?

1 ❑ change or difficulty in hearing
2 ❑ feeling of fullness in the ears
3 ❑ ringing, buzzing or noises in ears
4 ❑ Other (please indicate) _____
5 ❑ None

During the last 12 months , have you had any of the following symptoms which you think may be side effects caused by Tramadol (Zydol®) ? Only indicate the problems which were not present before you started taking **Tramadol (Zydol®)** .

17. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your mouth or gums ?

1 ❑ bleeding from gums
2 ❑ dry mouth or throat
3 ❑ Other (please indicate) _____
4 ❑ None

18. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your nose, throat, neck or voice?

1 ❑ difficulty talking
2 ❑ slurred speech
3 ❑ runny or stuffy nose
4 ❑ sore throat
5 ❑ Other (please indicate) _____
6 ❑ None

19. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your breathing or lungs?

1 ❑ cough
2 ❑ difficulty breathing
3 ❑ fast breathing
4 ❑ slow breathing
5 ❑ Other (please indicate) _____
6 ❑ None

20. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your heart or circulation?

1 ❑ palpitations/ racing heart
2 ❑ missed heart beat
3 ❑ Other (please indicate) _____
4 ❑ None

21. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your stomach or digestive system?

1 ❑ bloated feeling or gas
2 ❑ decrease in appetite
3 ❑ indigestion or heartburn
4 ❑ increase in appetite
5 ❑ pain or cramps in lower abdomen
6 ❑ nausea or vomiting
7 ❑ vomiting blood or material that looks like coffee grounds
8 ❑ Other (please indicate) _____
9 ❑ None

During the last 12 months , have you had any of the following symptoms which you think may be side effects caused by Tramadol (Zydol®) ? Only indicate the problems which were not present before you started taking **Tramadol (Zydol®)** .

22. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your rectum or bowel movements?

1 ❑ black tarry stool
2 ❑ constipation
3 ❑ diarrhoea
4 ❑ Other (please indicate) _____
5 ❑ None

23. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your kidneys, bladder or urinary system?

1 ❑ burning, discomfort or pain while passing water
2 ❑ dark brown urine
3 ❑ difficulty in passing water
4 ❑ passing water less often
5 ❑ passing water more often
6 ❑ bloody urine
7 ❑ Other (please indicate) _____
8 ❑ None

24. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your sexual function (ability)?

1 ❑ decrease in sexual desire
2 ❑ decrease in sexual ability
3 ❑ increase in sexual desire
4 ❑ Other (please indicate) _____
5 ❑ None
6 ❑ Does not apply

25. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your reproductive (sex) organ?

1 ❑ abnormal or change in vaginal bleeding
2 ❑ burning or irritated penis
3 ❑ Other (please indicate) _____
4 ❑ None

26. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your nervous system?

1 ❑ confusion or delirium
2 ❑ light-headed when getting up from a lying or sitting position or feeling faint
3 ❑ dizziness or staggering (vertigo)
4 ❑ increase in convulsions (seizures)
5 ❑ Other (please indicate) _____
6 ❑ None

During the last 12 months , have you had any of the following symptoms which you think may be side effects caused by Tramadol (Zydol®) ? Only indicate the problems which were not present before you started taking **Tramadol (Zydol®)** .

27. Have you had any of the following symptoms which you think may be due to side effects from this medicine related to your mental health?

1 ❑ anxiety (nervousness) or agitation
2 ❑ change in mood
3 ❑ difficulty concentrating or learning
4 ❑ hallucinations (seeing, hearing or feeling things that are not there)
5 ❑ nightmares
6 ❑ anger or aggression
7 ❑ loss of memory
8 ❑ thought of suicide
9 ❑ reduction in sleeping
10 ❑ increase sleep or drowsiness
11 ❑ Other (please indicate)
_____
12 ❑ None

28. Have you had any of the following symptoms which you think may be due to side effects from this medicine?

1 ❑ increased sensitivity to cold
2 ❑ excessive thirst
3 ❑ fever
4 ❑ flu-like symptoms
5 ❑ increase sweating
6 ❑ unusual tiredness or weakness
7 ❑ weight gain
8 ❑ weight loss
9 ❑ Other (please indicate)
_____
10 ❑ None

29. Which, if any, of the symptoms in question 11 - 29 have bothered you most ?

_____

30. How much has this symptom(s) in question 30 bothered you at its worst ?

1 ❑ minimally
2 ❑ mildly
3 ❑ moderately
4 ❑ severely
5 ❑ very severely
6 ❑ does not apply

31. Have you told your doctor about any of these symptom(s)?

1 ❑ all
2 ❑ some
3 ❑ none
4 ❑ I'm not sure
5 ❑ does not apply

Please ensure you have answered all questions in parts 1 and 2.

If you have stopped taking your medicine, please answer the questions overleaf.

Please return the completed questionnaire in the pre-paid envelope provided.

PART 3 : ONLY COMPLETE THIS SECTION IF YOU HAVE STOPPED TAKING Tramadol (Zydol®) .

32. When did you stop this medicine? (__ __ / __ __)
month / year

33. Why did you stop?

1 ❑ I felt I didn't need it any longer
2 ❑ The doctor said I didn't need it any longer
3 ❑ The doctor told me to stop because I was having problems with it
4 ❑ I decided to stop because I was having problems with it
5 ❑ I felt it wasn't helping me
6 ❑ Other (please explain) _____

_____

34. Have any of the symptoms you have described gone away?

1 ❑ Yes 2 ❑ No 3 ❑ Does not apply

If yes, please say which ones.

_____

_____

35. Have any other symptoms started after stopping **Tramadol (Zydol®)** ?

1 ❑ Yes 2 ❑ No

If yes, please describe them here.

_____

_____

Thank you for your time and co-operation.

Please return the completed questionnaire in the pre-paid envelope provided.

Number _____

Appendix G: Letter to senior general practitioners

8 August 1996

«ADDRESS»

Dear «NAME»

We are writing to you to ask for your co-operation in a study which aims to identify adverse drug reactions to new CNS drugs by patient self-monitoring. The drugs we are interested in are tramadol, fentanyl patch, moclobemide, citalopram, nefazodone, venlafaxine, lamotrigine, gabapentin, and topiramate because they are black triangle drugs. Reporting rates to the CSM are relatively low and this study is designed to evaluate patient self-monitoring as a method of increasing the reporting. All GPs in the Grampian area are being approached. We would like all your patients for whom you have prescribed these new drugs to complete a questionnaire. The questionnaire will ask your patients for demographic details, the other medicines they take, any symptoms they feel after taking the new medicine, and whether they have told you about any symptoms they have experienced.

The project team would particularly value your contribution and would be grateful if you would give your permission for questionnaires to be sent to your patients. The patients will be identified using prescription data from the Pharmacy Practice Division. We plan to compare the patients' perceived adverse reaction rates to the rates of reporting to the CSM. We would therefore also like your permission to obtain data from the CSM on any cases you have reported concerning the study drugs.

If you are happy for your patients to take part in this study, you need take no further action. However, if you wish to be excluded from the study, please complete and return the enclosed form as soon as possible, but no later than 31 August 1996.

With many thanks in anticipation on behalf of the project team.

Dr Janet Krska
Project Director

Project Team: Professor RME Richards (Head of School of Pharmacy), Dr P Capps (Lecturer/Practitioner), and Narumol Jarernsiripornkul (PhD Student, The Robert Gordon University)

The partners in _____ medical practice do not wish their patients to be included in the adverse drug reaction reporting study.

Signed _____

Status _____

Date _____

Please return to: Dr Janet Krska, Project Director, School of Pharmacy, The Robert Gordon University, Aberdeen AB9 1FR

Appendix H: Reminder letter to senior general practitioners

23rd May 1997

Dear Dr

You may recall that we wrote to you last year (ref. 24th June 1996) requesting your co-operation in a study we are conducting which aims to identify adverse reactions to black triangle CNS drugs. Reporting rates to the CSM are relatively low and this study is designed to evaluate the use of a patient self- completion questionnaire as a means of increasing the reporting. The drugs we are interested in are : tramadol, fentanyl patch, moclobemide, citalopram, nefazodone, venlafaxine, lamotrigine, gabapentin and topiramate. Patients taking these medicines will be identified using prescription data from the Pharmacy Practice Division.

All GP's in Grampian have been approached and 79 practices have opted to take part in the study. As one of those practices, we are taking this opportunity to inform you that patients in your practice who are currently taking one of the above medicines, will shortly receive one of the questionnaires to fill in. This has undergone piloting and we now enclose the final version for your information.

We must emphasise that any information provided by patients is entirely confidential and at their discretion. If any patient would like further information or reassurance before filling in the questionnaire, we will be happy to discuss the study with them (tel 01224 262500).

With many thanks for your help.

Yours sincerely

Dr Janet Krska
Project Director

On behalf of the Project Team : Professor RME Richards (Head of school of Pharmacy), Dr P Capps (Project Supervisor), Narumol Jarernsiripornkul (PhD Student)

Appendix I: Frequency of reported symptoms in pilot study

Table I.1 Frequency of symptoms reported by responden prescribed trazodone and doxepin

ADRs	number of patients (%)	
	Trazodone (n=41)	**Doxepin** (n=52)
skin		
bleeding	1 (2.4%)	-
bruising	4 (9.8%)	2 (3.8%)
burning sensation	3 (7.3%)	2 (3.8%)
flushing	4 (9.8%)	6 (11.5%)
photosensitivity	2 (4.9%)	-
itching	12 (29.3%)	4 (7.7%)
pale skin	3 (7.3%)	1 (1.9%)
puffy skin	3 (7.3%)	1 (1.9%)
pins and needles sensation	7 (17.1%)	7 (13.5%)
skin rash	4 (9.8%)	-
yellowing of skin	-	1 (1.9%)
other	2 (4.9%)	1 (1.9%)
none	20 (48.8%)	35 (67.3%)
hair or nails		
change in fingernails	2 (4.9%)	2 (3.8%)
hair loss	1 (2.4%)	2 (3.8%)
other	2 (4.9%)	-
none	33 (80.5%)	46 (88.5%)
muscles, bone and joints		
bone or joint pain	7 (17.1%)	4 (7.7%)
muscle pain	4 (9.8%)	5 (9.6%)
muscle weakness	3 (7.3%)	4 (7.7%)
trembling of fingers or hands	10 (24.4%)	4 (7.7%)
unsteadiness on feet	14 (34.1%)	4 (7.7%)
unusual body movement	2 (4.9%)	1 (1.9%)
none	18 (43.9%)	37 (71.2%)
head		
headache	2 (4.9%)	5 (9.6%)
migraine headache	4 (9.8%)	-
none	31 (75.6%)	45 (86.5%)
vision		
reduced vision	8 (19.5%)	4 (7.7%)
double vision	4 (9.8%)	1 (1.9%)
none	28 (68.3%)	44 (84.5%)

ADRs	number of patients (%)	
	Trazodone (n=41)	Doxepin (n=52)
eyes		
itchy or irritated or inflamed eyes	10 (24.4%)	7 (13.5%)
inability to move eyes	1 (2.4%)	-
unusual movement of eyes	1 (2.4%)	2 (3.8%)
none	28 (68.3%)	43 (82.7%)
hearing or ears		
change or difficulty in hearing	7 (17.1%)	2 (3.8%)
feeling or fullness in ears	2 (4.9%)	1 (1.9%)
ringing, buzzing or noises in ears	2 (4.9%)	9 (17.3%)
other	1 (2.4%)	-
none	29 (70.7%)	40 (76.9%)
mouth or gums		
bleeding from gums	1 (2.4%)	-
dry mouth or throat	20 (48.8%)	26 (50.0%)
none	20 (48.8%)	24 (46.2%)
nose, throat, neck or voice		
difficulty talking	2 (4.9%)	2 (3.8%)
slurred speech	4 (9.8%)	1 (1.9%)
runny or stuffy nose	11 (26.8%)	7 (13.5%)
sore throat	3 (7.3%)	1 (1.9%)
other	-	1 (1.9%)
none	23 (56.1%)	40 (76.9%)
breathing or lungs		
cough	5 (12.2%)	3 (5.8%)
difficulty breathing	5 (12.2%)	1 (1.9%)
fast breathing	7 (17.1%)	2 (3.8%)
slow breathing	1 (2.4%)	1 (1.9%)
other	1 (2.4%)	-
none	25 (61.0%)	44 (84.6%)
heart or circulation		
palpitations/racing heart	8 (19.5%)	9 (17.3%)
missed heart beat	1 (2.4%)	2 (3.8%)
other	1 (2.4%)	-
none	29 (70.7%)	41 (78.8%)

ADRs	number of patients (%)	
	Trazodone (n=41)	Doxepin (n=52)
stomach or digestive system		
bloated feeling or gas	5 (12.2%)	7 (13.5%)
decrease in appetite	5 (12.2%)	3 (5.8%)
indigestion or heartburn	6 (14.6%)	11 (21.2%)
increase in appetite	5 (12.2%)	7 (13.5%)
pain or cramps in lower abdomen	4 (9.8%)	1 (1.9%)
vomiting	1 (2.4%)	1 (1.9%)
vomiting blood	1 (2.4%)	-
none	23 (56.1%)	30 (57.7%)
rectum or bowel movements		
black tarry stool	1 (2.4%)	1 (1.9%)
constipation	13 (31.7%)	9 (17.3%)
diarrhoea	4 (9.8%)	2 (3.8%)
other	-	2 (3.8%)
none	22 (53.7%)	36 (69.2%)
kidneys, bladder or urinary system		
burning while passing water	2 (4.9%)	2 (3.8%)
dark brown urine	6 (14.6%)	4 (7.7%)
difficult in passing urine	1 (2.4%)	2 (3.8%)
passing water less often	6 (14.6%)	5 (9.6%)
passing water more often	8 (19.5%)	5 (9.6%)
other	-	1 (1.9%)
none	25 (61.0%)	39 (75.0%)
sexual function		
decrease in sexual desire	9 (22.0%)	7 (13.5%)
decrease in sexual ability	3 (7.3%)	2 (3.8%)
increase in sexual desire	1 (2.4%)	2 (3.8%)
other	-	-
none	26 (63.4%)	41 (78.8%)
sexual organ		
burning or irritated penis	1 (6.6%)*	1 (7.1%)*
other	1 (2.4%)	1 (1.9%)
none	35 (85.4%)	44 (84.6%)
nervous system		
confusion or delirium	4 (9.8%)	2 (3.8%)
light-headed or hypotension	16 (39.0%)	9 (17.3%)
dizziness or staggering	10 (24.4%)	6 (11.5%)
increase in convulsion	-	1 (1.9%)
other	1 (2.4%)	-
none	18 (43.9%)	37 (71.2%)

ADRs	number of patients (%)	
	Trazodone (n=41)	Doxepin (n=52)
mental health		
anxiety(nervousness)or agitation	19 (46.3%)	4 (7.7%)
change in mood	12 (29.3%)	4 (7.7%)
difficulty concentrating or learning	13 (31.7%)	7 (13.5%)
hallucinations	1 (2.4%)	1 (1.9%)
anger	6 (14.3%)	7 (13.4%)
loss of memory	9 (22.0%)	6 (11.5%)
thought of suicide	2 (4.9%)	2 (3.8%)
reduction in sleeping	8 (19.5%)	4 (7.7%)
increase sleep or drowsiness	17 (41.5%)	10 (19.2%)
other	1 (2.4%)	-
none	5 (12.2%)	23 (44.2%)
other ADRs		
increase sensitivity to cold	9 (22.2%)	3 (5.8%)
excessive thirst	12 (29.3%)	9 (17.3%)
fever	-	-
flu-like symptoms	-	1 (1.9%)
hot flush	2 (4.9%)	1 (1.9%)
increase sweating	3 (7.3%)	4 (7.7%)
unusual tiredness or weakness	14 (34.1%)	9 (17.3%)
weight gain	11 (26.8%)	9 (17.3%)
weight loss	2 (4.9%)	2 (3.8%)
none	11 (26.8%)	24 (46.2%)

* denominator = number of male respondents

Table I.2 Frequency of symptoms reported by patients prescribed sodium valproate and carbamazepine

ADRs	number of patients (%)	
	Valproate (n=25)	**Carbamazepine** (n=44)
skin		
bleeding	1 (4.0%)	1 (2.3%)
bruising	2 (8.0%)	1 (2.3%)
burning sensation	1 (4.0%)	1 (2.3%)
flushing	3 (12.0%)	-
photosensitivity	1 (4.0%)	-
itching	1 (4.0%)	5 (11.4%)
pale skin	2 (8.0%)	3 (6.8%)
puffy skin	-	-
pins and needles sensation	3 (12.0%)	2 (4.5%)
skin rash	3 (12.0%)	3 (6.8%)
yellowing of skin	-	-
other	2 (8.0%)	1 (2.3%)
none	15 (60.0%)	31 (70.5%)
hair or nails		
change in fingernails	3 (12.0%)	1 (2.3%)
hair loss	7 (28.0%)	2 (4.5%)
other	1 (4.0%)	-
none	15 (60.0%)	37 (84.1%)
muscles, bone and joints		
bone or joint pain	5 (20.0%)	4 (9.1%)
muscle pain	4 (16.0%)	6 (13.6%)
muscle weakness	4 (16.0%)	3 (6.8%)
trembling of fingers or hands	11 (44.0%)	9 (20.5%)
unsteadiness on feet	5 (20.0%)	6 (13.6%)
unusual body movement	1 (4.0%)	1 (2.3%)
other	1 (4.0%)	-
none	6 (24.0%)	22 (50.0%)
head		
headache	6 (24.0%)	7 (15.9%)
migraine headache	4 (16.0%)	6 (13.6%)
none	13 (52.0%)	32 (72.7%)
vision		
reduced vision	3 (12.0%)	10 (22.7%)
double vision	3 (12.0%)	7 (15.9%)
other	-	-
none	19 (76.0%)	28 (63.6%)

Table I.2 Frequency of symptoms reported by patients prescribed sodium valproate and carbamazepine

ADRs	number of patients (%)	
	Valproate (n=25)	**Carbamazepine** (n=44)
skin		
bleeding	1 (4.0%)	1 (2.3%)
bruising	2 (8.0%)	1 (2.3%)
burning sensation	1 (4.0%)	1 (2.3%)
flushing	3 (12.0%)	-
photosensitivity	1 (4.0%)	-
itching	1 (4.0%)	5 (11.4%)
pale skin	2 (8.0%)	3 (6.8%)
puffy skin	-	-
pins and needles sensation	3 (12.0%)	2 (4.5%)
skin rash	3 (12.0%)	3 (6.8%)
yellowing of skin	-	-
other	2 (8.0%)	1 (2.3%)
none	15 (60.0%)	31 (70.5%)
hair or nails		
change in fingernails	3 (12.0%)	1 (2.3%)
hair loss	7 (28.0%)	2 (4.5%)
other	1 (4.0%)	-
none	15 (60.0%)	37 (84.1%)
muscles, bone and joints		
bone or joint pain	5 (20.0%)	4 (9.1%)
muscle pain	4 (16.0%)	6 (13.6%)
muscle weakness	4 (16.0%)	3 (6.8%)
trembling of fingers or hands	11 (44.0%)	9 (20.5%)
unsteadiness on feet	5 (20.0%)	6 (13.6%)
unusual body movement	1 (4.0%)	1 (2.3%)
other	1 (4.0%)	-
none	6 (24.0%)	22 (50.0%)
head		
headache	6 (24.0%)	7 (15.9%)
migraine headache	4 (16.0%)	6 (13.6%)
none	13 (52.0%)	32 (72.7%)
vision		
reduced vision	3 (12.0%)	10 (22.7%)
double vision	3 (12.0%)	7 (15.9%)
other	-	-
none	19 (76.0%)	28 (63.6%)

ADRs	number of patients (%)	
	Valproate (n=25)	Carbamazepine (n=44)
eyes		
itchy or irritated or inflamed eyes	2 (8.0%)	6 (113.6%)
inability to move eyes	-	1 (2.3%)
unusual movement of eyes	2 (8.0%)	2 (4.5%)
none	19 (76.0%)	36 (81.8%)
hearing or ears		
change or difficulty in hearing	1 (4.0%)	2 (4.5%)
feeling or fullness in ears	-	2 (4.5%)
ringing, buzzing or noises in ears	4 (16.0%)	2 (4.5%)
none	18 (72.0%)	36 (81.8%)
mouth or gums		
bleeding from gums	1 (4.0%)	-
dry mouth or throat	4 (16.0%)	7 (15.9%)
none	18 (72.0%)	35 (79.5%)
nose, throat, neck or voice		
difficulty talking	-	2 (4.5%)
slurred speech	2 (8.0%)	4 (9.1%)
runny or stuffy nose	5 (20.0%)	3 (6.8%)
sore throat	4 (16.0%)	3 (6.8%)
other	1 (4.0%)	1 (2.3%)
none	15 (60.0%)	29 (65.9%)
breathing or lungs		
cough	2 (8.0%)	3 (6.8%)
difficulty breathing	2 (8.0%)	-
fast breathing	1 (4.0%)	1 (2.3%)
slow breathing	1 (4.0%)	1 (2.3%)
none	16 (64.0%)	36 (81.8%)
heart or circulation		
palpitations/racing heart	2 (8.0%)	6 (13.6%)
missed heart beat	-	1 (2.3%)
none	19 (76.0%)	33 (75.0%)

ADRs	number of patients (%)	
	Valproate (n=25)	Carbamazepine (n=44)
stomach or digestive system		
bloated feeling or gas	5 (20.0%)	2 (4.5%)
decrease in appetite	5 (20.0%)	3 (6.8%)
indigestion or heartburn	6 (24.0%)	6 (13.6%)
increase in appetite	5 (20.0%)	4 (9.1%)
pain or cramps in lower abdomen	3 (12.0%)	2 (4.5%)
vomiting	3 (12.0%)	3 (6.8%)
vomiting blood	-	1 (2.3%)
none	10 (40.0%)	26 (59.1%)
rectum or bowel movements		
black tarry stool	2 (8.0%)	-
constipation	4 (16.0%)	6(13.6%)
diarrhoea	7 (28.0%)	2(4.5%)
none	15 (60.0%)	33 (75.0%)
kidneys, bladder or urinary system		
burning while passing water	1 (4.0%)	1 (2.3%)
dark brown urine	2 (8.0%)	1 (2.3%)
difficult in passing urine	1 (4.0%)	-
passing water less often	1 (4.0%)	3 (6.8%)
passing water more often	6 (24.0%)	6 (13.6%)
bloody urine	-	-
none	13 (52.0%)	30 (68.2%)
sexual function		
decrease in sexual desire	4 (16.0%)	5 (11.4%)
decrease in sexual ability	5 (20.0%)	1 (2.3%)
increase in sexual desire	1 (4.0%)	2 (4.5%)
other	1 (4.0%)	-
none	14 (56.0%)	33 (75.0%)
sexual organ		
abnormal vaginal bleeding	-	-
burning or irritated penis	1 (14.3%)*	-
other	2 (8.0%)	-
none	17 (68.0%)	41 (93.2%)
nervous system		
confusion or delirium	4 (16.0%)	3 (6.8%)
light-headed or hypotension	4 (16.0%)	9 (20.5%)
dizziness or staggering	3 (12.0%)	8 (18.2%)
increase in convulsion	1 (4.0%)	5 (11.4%)
other	-	1 (2.3%)
none	12 (48.0%)	26 (59.1%)

ADRs	number of patients (%)	
	Valproate (n=25)	Carbamazepine (n=44)
mental health		
anxiety(nervousness)or agitation	6 (24.0%)	4 (9.1%)
change in mood	6 (24.0%)	4 (9.1%)
difficulty concentrating or learning	9 (36.0%)	10 (22.7%)
hallucinations	-	-
anger	5 (20.0%)	4 (9.1%)
loss of memory	9 (36.0%)	8 (18.2%)
thought of suicide	1 (4.0%)	1 (2.3%)
reduction in sleeping	4 (16.0%)	6 (13.6%)
increase sleep or drowsiness	8 (32.0%)	15 (34.1%)
other	-	1 (2.3%)
none	5 (20.0%)	17 (38.6%)
other ADRs		
increase sensitivity to cold	6 (24.0%)	5 (11.4%)
excessive thirst	2 (8.0%)	3 (6.8%)
fever	-	-
flu-like symptoms	2 (8.0%)	-
increase sweating	4(16.0%)	1 (2.3%)
unusual tiredness or weakness	14 (56.0%)	12 (27.3%)
weight gain	6 (24.0%)	4 (9.1%)
other	-	-
none	8 (32.0%)	22 (50.0%)

* denominator = number of male respondents

Table I.3 frequency of symptoms reported by respondents prescribed co-proxamol

ADRs	number of patients (%)
	Co-proxamol (n=45)
skin	
bleeding	2 (4.4%)
bruising	3 (6.7%)
burning sensation	2 (4.4%)
flushing	10 (22.2%)
photosensitivity	-
itching	9 (20.0%)
pale skin	2 (4.4%)
pins and needles sensation	6 (13.3%)
skin rash	3 (6.7%)
yellowing of skin	4 (8.8%)
other	3 (6.7%)
none	24 (53.3%)
hair or nails	
change in fingernails	9 (20.0%)
hair loss	5 (11.1%)
none	30 (66.7%)
muscles, bone and joints	
bone or joint pain	6 (13.3%)
muscle pain	3 (6.7%)
muscle weakness	2 (4.4%)
trembling of fingers or hands	4 (8.9%)
unsteadiness on feet	7 (15.6%)
unusual body movement	1 (2.2%)
none	32 (71.1%)
head	
headache	4 (8.9%)
migraine headache	3 (6.7%)
none	35 (77.8%)
vision	
reduced vision	4 (8.9%)
double vision	-
none	37 (82.2%)

ADRs	number of patients (%)
	Co-proxamol (n=45)
eyes	
itchy or irritated or inflamed eyes	10 (22.2%)
inability to move eyes	-
unusual movement of eyes	1 (2.2%)
none	1 (2.2%)
hearing or ears	
change or difficulty in hearing	4 (8.9%)
feeling or fullness in ears	2 (4.4%)
ringing, buzzing or noises in ears	4 (8.9%)
none	35 (77.8%)
mouth or gums	
bleeding from gums	1 (2.2%)
dry mouth or throat	10 (22.2%)
none	31 (68.9%)
nose, throat, neck or voice	
difficulty talking	2 (4.4%)
slurred speech	1 (2.2%)
runny or stuffy nose	3 (6.7%)
sore throat	3 (6.7%)
other	1 (2.2%)
none	34 (75.6%)
breathing or lungs	
cough	3 (6.7%)
difficulty breathing	3 (6.7%)
fast breathing	2 (4.4%)
slow breathing	-
none	34 (75.6%)
heart or circulation	
palpitations/racing heart	4 (8.9%)
missed heart beat	1 (2.2%)
none	35 (77.8%)

ADRs	number of patients (%)
	Co-proxamol (n=45)
stomach or digestive system	
bloated feeling or gas	6 (13.3%)
decrease in appetite	5 (11.1%)
indigestion or heartburn	7 (15.6%)
increase in appetite	2 (4.4%)
pain or cramps in lower abdomen	6 (13.3%)
vomiting	1 (2.2%)
vomiting blood	-
none	29 (64.4%)
rectum or bowel movements	
black tarry stool	1 (2.2%)
constipation	11 (24.4%)
diarrhoea	3 (6.7%)
none	30 (66.7%)
kidneys, bladder or urinary system	
burning while passing water	2 (4.4%)
dark brown urine	4 (8.9%)
difficult in passing urine	1 (2.2%)
passing water less often	1 (2.2%)
passing water more often	7 (15.6%)
none	32 (71.1%)
sexual function	
decrease in sexual desire	7 (15.6%)
decrease in sexual ability	2 (4.4%)
increase in sexual desire	-
none	32 (71.1%)
sexual organ	
burning or irritated penis	1 (6.25%)*
other	1 (2.2%)
none	39 (86.7%)
nervous system	
confusion or delirium	1 (2.2%)
light-headed or hypotension	6 (13.3%)
dizziness or staggering	8 (17.8%)
increase in convulsion	-
none	33 (73.3%)

ADRs	number of patients (%)
	Co-proxamol (n=45)
mental health	
anxiety(nervousness)or agitation	5 (11.1%)
change in mood	4 (8.9%)
difficulty concentrating or learning	5 (11.1%)
hallucinations	3 (6.7%)
anger	2 (4.4%)
loss of memory	5 (11.1%)
thought of suicide	3 (6.7%)
reduction in sleeping	6 (13.3%)
increase sleep or drowsiness	4 (8.9%)
none	24 (53.3%)
other ADRs	
increase sensitivity to cold	9 (20.0%)
excessive thirst	7 (15.6%)
fever	1 (2.2%)
flu-like symptoms	2 (4.4%)
increase sweating	5 (11.1%)
unusual tiredness or weakness	7 (15.6%)
weight gain	3 (6.7%)
weight loss	1 (2.2%)
none	

* denominator = number of male respondents

Appendix J: Frequency of reported symptoms in main study

Table J.1 Frequency of symptoms reported by patients prescribed tramadol and fentanyl patch

Symptom	Number of patients (%)	
	Tramadol (n=344)	**Fentanyl Patch** (n=8)
skin		
bleeding	5 (1.5%)	---
bruising	14 (4.1%)	---
burning sensation	18 (5.2%)	---
flushing	67 (19.5%)	1 (12.5%)
photosensitivity	4 (1.2%)	---
itching	65 (18.9%)	3 (37.5%)
pale skin	7 (2.0%)	---
puffy skin	11 (3.2%)	1 (12.5%)
pins and needles sensation	46 (13.4%)	---
skin rash	20 (5.8%)	---
yellowing of skin	4 (1.2%)	---
other	---	2 (25.0%)
none	194 (56.4%)	3 (37.5%)
hair or nails		
change in fingernails	28 (8.1%)	---
hair loss	22 (6.4%)	---
other	3 (0.9%)	---
none	273 (79.4%)	8 (100%)
muscles, bone and joints		
bone or joint pain	37 (10.8%)	---
muscle pain	30 (8.7%)	1 (12.5%)
muscle weakness	27 (7.8%)	2 (25.0%)
trembling of fingers or hands	45 (13.1%)	---
unsteadiness on feet	54 (15.7%)	3 (37.5%)
unusual body movement	13 (3.8%)	---
other	---	---
none	226 (65.7%)	4 (50.0%)
head		
headache	40 (11.6%)	1 (12.5%)
migraine headache	17 (4.9%)	1 (12.5%)
other	---	---
none	263 (76.5%)	4 (50.0%)
vision		
blurred vision	40 (11.6%)	2 (25.0%)
double vision	4 (1.2%)	1 (12.5%)
other	---	---
none	272 (79.1%)	4 (50.0%)

Symptom	Number of patients (%)	
	Tramadol (n=344)	Fentanyl Patch (n=8)
eyes		
itchy or irritated or inflamed eyes	49 (14.2%)	---
inability to move eyes	1 (0.3%)	---
unusual movement of eyes	4 (1.2%)	---
other	1 (0.3%)	---
none	266 (77.3%)	7 (87.5%)
hearing or ears		
change or difficulty in hearing	26 (7.6%)	---
feeling or fullness in ears	12 (3.5%)	1 (12.5%)
ringing, buzzing or noises in ears	40 (11.6%)	1 (12.5%)
other	2 (0.6%)	---
none	257 (74.7%)	5 (62.5%)
mouth or gums		
bleeding from gums	5 (1.5%)	---
dry mouth or throat	112 (32.6%)	3 (37.5%)
other	206 (59.9%)	---
none	6 (1.7%)	4 (50.0%)
nose, throat, neck or voice		
difficulty talking	8 (2.3%)	---
slurred speech	15 (4.4%)	---
runny or stuffy nose	44 (12.8%)	2 (25.0%)
sore throat	16 (4.7%)	---
other	2 (0.6%)	---
none	245 (71.2%)	4 (50.0%)
breathing or lungs		
cough	10 (2.9%)	1 (12.5%)
difficulty breathing	10 (2.9%)	3 (37.5%)
fast breathing	11 (3.2%)	---
slow breathing	3 (0.9%)	1 (12.5%)
other	---	---
none	281 (81.7%)	3 (37.5%)
heart or circulation		
palpitations/racing heart	29 (8.4%)	---
missed heart beat	9 (2.6%)	---
other	---	---
none	277 (80.5%)	6 (75.0%)

Symptom	Number of patients (%)	
	Tramadol (n=344)	Fentanyl Patch (n=8)
stomach or digestive system		
bloated feeling or gas	45 (13.1%)	2 (25.0%)
decrease in appetite	37 (10.8%)	4 (50.0%)
indigestion or heartburn	54 (15.7%)	2 (25.0%)
increase in appetite	10 (2.9%)	---
pain or cramps in lower abdomen	39 (11.3%)	3 (37.5%)
nausea or vomiting	66 (19.2%)	4 (50.0%)
vomiting blood	7 (2.0%)	1 (12.5%)
other	---	---
none	171 (49.7%)	1 (12.5%)
rectum or bowel movements		
black tarry stool	10 (2.9%)	1 (12.5%)
constipation	84 (24.4%)	5 (62.5%)
diarrhoea	25 (7.3%)	---
other	2 (0.6%)	---
none	222 (64.5%)	2 (25.0%)
kidneys, bladder or urinary system		
burning while passing water	17 (4.9%)	1 (12.5%)
dark brown urine	19 (5.5%)	---
difficult in passing urine	25 (7.3%)	---
passing water less often	13 (3.8%)	1 (12.5%)
passing water more often	40 (11.6%)	1 (12.5%)
bloody urine	4 (1.2%)	---
other	2 (0.6%)	---
none	232 (67.4%)	5 (12.5%)
sexual function		
decrease in sexual desire	30 (8.7%)	3 (37.5%)
decrease in sexual ability	21 (6.1%)	1 (12.5%)
increase in sexual desire	3 (0.9%)	---
other	---	---
none	162 (47.1%)	2 (25.0%)
does not apply	120 (34.9%)	3 (37.5%)
sexual organ		
abnormal vaginal bleeding	8 (3.5%)*	---
burning or irritated penis	4 (3.5%)**	---
other	1 (0.3%)	---
none	301 (87.5%)	7 (87.5%)

Symptom	Number of patients (%)	
	Tramadol (n=344)	Fentanyl Patch (n=8)
nervous system		
confusion or delirium	13 (3.8%)	1 (12.5%)
light-headed or hypotension	85 (24.7%)	3 (37.5%)
dizziness or staggering	56 (16.3%)	1 (12.5%)
increase in convulsion	4 (1.2%)	---
other	---	---
none	211 (61.3%)	4 (50.0%)
mental health		
anxiety(nervousness)or agitation	37 (10.8%)	2 (25.0%)
change in mood	40 (11.6%)	2 (25.0%)
difficulty concentrating or learning	27 (7.8%)	1 (25.0%)
hallucinations	8 (2.3%)	---
nightmares	21 (6.1%)	---
anger	27 (7.8%)	2 (25.0%)
loss of memory	20 (5.8%)	2 (25.0%)
thought of suicide	6 (1.7%)	---
reduction in sleeping	49 (14.2%)	2 (25.0%)
increase sleep or drowsiness	70 (20.3%)	2 (25.0%)
other	---	---
none	171 (49.7%)	3 (37.5%)
other ADRs		
increase sensitivity to cold	28 (8.1%)	3 (37.5%)
excessive thirst	46 (13.4%)	3 (37.5%)
fever	5 (1.5%)	---
flu-like symptoms	10 (2.9%)	1 (12.5%)
increase sweating	69 (20.1%)	3 (37.5%)
unusual tiredness or weakness	65 (18.9%)	3 (37.5%)
weight gain	29 (8.4%)	---
weight loss	16 (4.7%)	4 (50.0%)
other	---	---
none	163 (47.4%)	2 (25.0%)

* denominator = number of female respondents
** denominator = number of male respondents

Table J.2 Frequency of symptoms reported by patients prescribed venlafaxine and nefazodone

Symptom	Number of patients (%)	
	Venlafaxine (n=263)	Nefazodone (n=64)
skin		
bleeding	3 (1.1%)	1 (1.6%)
bruising	23 (8.7%)	2 (3.1%)
burning sensation	10 (3.8%)	3 (4.7%)
flushing	78 (29.7%)	10 (15.6%)
photosensitivity	11 (4.2%)	6 (9.4%)
itching	52 (19.8%)	10 (15.6%)
pale skin	11 (4.2%)	2 (3.1%)
puffy skin	14 (5.3%)	3 (4.7%)
pins and needles sensation	46 (17.5%)	19 (29.7%)
skin rash	15 (5.7%)	2 (3.1%)
yellowing of skin	3 (1.1%)	---
other	4 (1.5%)	2 (3.1%)
none	119 (45.2%)	30 (46.9%)
hair or nails		
change in fingernails	19 (7.2%)	8 (12.5%)
hair loss	21 (8.0%)	4 (6.3%)
other	4 (1.5%)	1 (1.6%)
none	208 (79.1%)	52 (81.3%)
muscles, bone and joints		
bone or joint pain	29 (11.0%)	13 (20.3%)
muscle pain	26 (9.9%)	8 (12.5%)
muscle weakness	17 (6.5%)	9 (14.1%)
trembling of fingers or hands	56 (21.3%)	16 (25.0%)
unsteadiness on feet	41 (15.6%)	14 (21.9%)
unusual body movement	17 (6.5%)	4 (6.3%)
other	1 (0.4%)	---
none	150 (57.0%)	31 (48.4%)
head		
headache	50 (19.0%)	15 (23.4%)
migraine headache	17 (6.5%)	1 (1.6%)
other	---	---
none	192 (73.0%)	47 (73.4%)
vision		
blurred vision	44 (16.7%)	11 (17.2%)
double vision	5 (1.9%)	1 (1.6%)
other	2 (0.8%)	---
none	205 (77.9%)	48 (75.0%)

Symptom	Number of patients (%)	
	Venlafaxine (n=263)	Nefazodone (n=64)
eyes		
itchy or irritated or inflamed eyes	36 (13.7%)	9 (14.1%)
inability to move eyes	5 (1.9%)	---
unusual movement of eyes	9 (3.4%)	2 (3.1%)
other	9 (3.4%)	3 (4.7%)
none	205 (72.9%)	49 (76.6%)
hearing or ears		
change or difficulty in hearing	19 (7.2%)	7 (10.9%)
feeling or fullness in ears	16 (6.1%)	3 (4.7%)
ringing, buzzing or noises in ears	37 (14.1%)	10 (15.6%)
other	2 (0.8%)	---
none	194 (73.8%)	42 (65.6%)
mouth or gums		
bleeding from gums	4 (1.5%)	2 (3.1%)
dry mouth or throat	121 (46.0%)	29 (45.3%)
other	9 (3.4%)	---
none	125 (47.5%)	32 (50.0%)
nose, throat, neck or voice		
difficulty talking	13 (4.9%)	1 (1.6%)
slurred speech	23 (8.7%)	7 (10.9%)
runny or stuffy nose	36 (13.7%)	12 (18.8%)
sore throat	17 (6.5%)	6 (9.4%)
other	2 (0.6%)	---
none	187 (71.1%)	45 (70.3%)
breathing or lungs		
cough	11 (4.2%)	4 (6.3%)
difficulty breathing	19 (7.2%)	3 (4.7%)
fast breathing	18 (6.8%)	3 (4.7%)
slow breathing	6 (2.3%)	1 (1.6%)
other	1 (0.4%)	---
none	206 (78.3%)	53 (82.8%)
heart or circulation		
palpitations/racing heart	58 (22.1%)	13 (20.3%)
missed heart beat	13 (4.9%)	3 (4.7%)
other	1 (0.4%)	---
none	189 (71.9%)	48 (75.0%)

Symptom	Number of patients (%)	
	Venlafaxine (n=263)	Nefazodone (n=64)
stomach or digestive system		
bloated feeling or gas	63 (24.0%)	12 (18.8%)
decrease in appetite	37 (14.1%)	13 (20.3%)
indigestion or heartburn	36 (13.7%)	13 (20.3%)
increase in appetite	38 (14.4%)	6 (9.4%)
pain or cramps in lower abdomen	28 (10.6%)	11 (17.2%)
nausea or vomiting	64 (24.3%)	14 (21.9%)
vomiting blood	1 (0.4%)	1 (1.6%)
other	---	---
none	103 (39.2%)	22 (34.4%)
rectum or bowel movements		
black tarry stool	3 (1.1%)	3 (4.7%)
constipation	71 (27.0%)	11 (17.2%)
diarrhoea	22 (8.4%)	12 (18.8%)
other	1 (0.4%)	---
none	167 (63.5%)	41 (64.1%)
kidneys, bladder or urinary system		
burning while passing water	7 (2.7%)	2 (3.1%)
dark brown urine	10 (3.8%)	6 (9.4%)
difficult in passing urine	7 (2.7%)	2 (3.1%)
passing water less often	14 (5.3%)	2 (3.1%)
passing water more often	33 (12.5%)	8 (12.5%)
bloody urine	2 (0.8%)	1 (1.6%)
other	3 (1.1%)	1 (1.6%)
none	185 (70.3%)	41 (64.1%)
sexual function		
decrease in sexual desire	89 (33.8%)	17 (26.6%)
decrease in sexual ability	50 (19.0%)	7 (10.9%)
increase in sexual desire	12 (4.6%)	4 (6.3%)
other	---	---
none	84 (31.9%)	27 (42.2%)
does not apply	54 (20.5%)	11 (17.2%)
sexual organ		
abnormal vaginal bleeding	13 (7.1%)*	1 (2.6%)*
burning or irritated penis	2 (2.6%)**	2 (8.0%)**
other	2 (0.8%)	---
none	232 (88.2%)	57 (89.1%)

Symptom	Number of patients (%)	
	Venlafaxine (n=263)	Nefazodone (n=64)
nervous system		
confusion or delirium	20 (7.6%)	7 (10.9%)
light-headed or hypotension	91 (34.6%)	22 (34.4%)
dizziness or staggering	48 (18.3%)	17 (26.6%)
increase in convulsion	---	---
other	---	---
none	138 (52.5%)	33 (51.6%)
mental health		
anxiety(nervousness)or agitation	59 (22.4%)	16 (25.0%)
change in mood	66 (25.1%)	14 (21.9%)
difficulty concentrating or learning	59 (22.4%)	20 (31.3%)
hallucinations	12 (4.6%)	4 (6.3%)
nightmares	39 (14.8%)	4 (6.3%)
anger	29 (11.0%)	7 (10.9%)
loss of memory	44 (16.7%)	13 (20.3%)
thought of suicide	20 (7.6%)	9 (14.1%)
reduction in sleeping	64 (24.3%)	19 (29.7%)
increase sleep or drowsiness	45 (17.1%)	12 (18.8%)
other	4 (1.5%)	---
none	91 (34.6%)	19 (29.7%)
other ADRs		
increase sensitivity to cold	23 (8.7%)	9 (14.1%)
excessive thirst	68 (25.9%)	13 (20.3%)
fever	---	1 (1.6%)
flu-like symptoms	11 (4.2%)	5 (7.8%)
increase sweating	107 (40.7%)	10 (15.6%)
unusual tiredness or weakness	88 (33.5%)	24 (37.5%)
weight gain	70 (26.6%)	12 (18.8%)
weight loss	20 (7.6%)	7 (10.9%)
other	1 (0.4%)	---
none	64 (24.3%)	21 (32.8%)

* denominator = number of female respondents
** denominator = number of male respondents

Table J.3 Frequency of symptoms reported by patients prescribed citalopram and moclobemide

Symptom	Number of patients (%)	
	Citalopam (n=43)	**Moclobemide** (n=16)
skin		
bleeding	---	---
bruising	2 (4.7%)	---
burning sensation	2 (4.7%)	---
flushing	10 (23.3%)	---
photosensitivity	1 (2.3%)	1 (6.3%)
itching	5 (11.6%)	2 (12.5%)
pale skin	3 (7.0%)	---
puffy skin	2 (4.7%)	---
pins and needles sensation	7 (16.3%)	1 (6.3%)
skin rash	4 (9.3%)	---
yellowing of skin	1 (2.3%)	---
other	1 (2.3%)	---
none	26 (60.5%)	13 (81.3%)
hair or nails		
change in fingernails	5 (11.6%)	---
hair loss	3 (7.0%)	---
other	---	---
none	36 (83.7%)	16 (100%)
muscles, bone and joints		
bone or joint pain	2 (4.7%)	---
muscle pain	3 (7.0%)	---
muscle weakness	3 (7.0%)	1 (6.3%)
trembling of fingers or hands	13 (30.2%)	1 (6.3%)
unsteadiness on feet	6 (14.0%)	2 (12.5%)
unusual body movement	3 (7.0%)	---
other	---	---
none	25 (58.1%)	12 (75.0%)
head		
headache	11 (25.6%)	5 (31.3%)
migraine headache	2 (4.7%)	2 (12.5%)
other	---	---
none	28 (65.1%)	9 (56.3%)
vision		
blurred vision	6 (14.0%)	---
double vision	2 (4.7%)	1 (6.3%)
other	---	1 (6.3%)
none	34 (79.1%)	14 (87.5%)

Symptom	Number of patients (%)	
	Citalopam (n=43)	Moclobemide (n=16)
eyes		
itchy or irritated or inflamed eyes	3 (7.0%)	2 (12.5%)
inability to move eyes	---	1 (6.3%)
unusual movement of eyes	---	1 (6.3%)
other	---	---
none	36 (83.7%)	10 (62.5%)
hearing or ears		
change or difficulty in hearing	5 (11.6%)	---
feeling or fullness in ears	2 (4.7%)	1 (6.3%)
ringing, buzzing or noises in ears	8 (18.6%)	1 (6.3%)
other	---	---
none	32 (74.4%)	14 (87.5%)
mouth or gums		
bleeding from gums	---	---
dry mouth or throat	16 (37.2%)	6 (37.5%)
other	1 (2.3%)	1 (6.3%)
none	24 (55.8%)	10 (62.5%)
nose, throat, neck or voice		
difficulty talking	---	---
slurred speech	3 (7.0%)	---
runny or stuffy nose	4 (9.3%)	1 (6.3%)
sore throat	1 (2.3%)	1 (6.3%)
other	---	---
none	36 (83.7%)	14 (87.5%)
breathing or lungs		
cough	6 (14.0%)	---
difficulty breathing	2 (4.7%)	2 (12.5%)
fast breathing	2 (4.7%)	---
slow breathing	---	---
other	---	---
none	33 (76.7%)	14 (87.5%)
heart or circulation		
palpitations/racing heart	6 (14.0%)	4 (25.0%)
missed heart beat	3 (7.0%)	---
other	---	---
none	35 (81.4%)	12 (75.0%)

Symptom	Number of patients (%)	
	Citalopam (n=43)	Moclobemide (n=16)
stomach or digestive system		
bloated feeling or gas	5 (11.6%)	2 (12.5%)
decrease in appetite	6 (14.0%)	2 (12.5%)
indigestion or heartburn	6 (14.0%)	1 (6.3%)
increase in appetite	1 (2.3%)	1 (6.3%)
pain or cramps in lower abdomen	6 (14.0%)	2 (12.5%)
nausea or vomiting	8 (18.6%)	3 (18.8%)
vomiting blood	1 (2.3%)	---
other	---	---
none	25 (58.1%)	9 (56.3%)
rectum or bowel movements		
black tarry stool	2 (4.7%)	---
constipation	8 (18.6%)	1 (6.3%)
diarrhoea	3 (7.0%)	1 (6.3%)
other	---	---
none	30 (69.8%)	14 (87.5%)
kidneys, bladder or urinary system		
burning while passing water	2 (4.7%)	---
dark brown urine	1 (2.3%)	---
difficult in passing urine	1 (2.3%)	---
passing water less often	2 (4.7%)	---
passing water more often	5 (11.6%)	2 (12.5%)
bloody urine	1 (2.3%)	---
other	1 (2.3%)	1 (6.3%)
none	33 (76.7%)	13 (81.3%)
sexual function		
decrease in sexual desire	10 (23.3%)	3 (18.8%)
decrease in sexual ability	7 (16.3%)	2 (12.5%)
increase in sexual desire	2 (4.7%)	---
other	---	---
none	15 (34.9%)	9 (56.3%)
does not apply	14 (32.6%)	3 (18.8%)
sexual organ		
abnormal vaginal bleeding	---	2 (15.4%)*
burning or irritated penis	---	---
other	1 (2.3%)	1 (2.3%)
none	37 (86.0%)	14 (87.5%)

Symptom	Number of patients (%)	
	Citalopam (n=43)	Moclobemide (n=16)
nervous system		
confusion or delirium	3 (7.0%)	3 (18.8%)
light-headed or hypotension	15 (34.9%)	1 (6.3%)
dizziness or staggering	6 (14.0%)	4 (25.0%)
increase in convulsion	---	---
other	---	---
none	25 (58.1%)	10 (62.5%)
mental health		
anxiety(nervousness)or agitation	9 (20.9%)	2 (12.5%)
change in mood	4 (9.3%)	2 (12.5%)
difficulty concentrating or learning	3 (7.0%)	3 (18.8%)
hallucinations	---	---
nightmares	1 (2.3%)	3 (18.8%)
anger	3 (7.0%)	1 (6.3%)
loss of memory	7 (16.3%)	3 (18.8%)
thought of suicide	2 (4.7%)	---
reduction in sleeping	7 (16.3%)	4 (25.0%)
increase sleep or drowsiness	14 (32.6%)	2 (12.5%)
other	1 (2.3%)	---
none	17 (39.5%)	7 (43.8%)
other ADRs		
increase sensitivity to cold	4 (9.3%)	3 (18.8%)
excessive thirst	6 (14.0%)	1 (6.3%)
fever	---	---
flu-like symptoms	1 (2.3%)	---
increase sweating	12 (27.9%)	2 (12.5%)
unusual tiredness or weakness	14 (32.6%)	3 (18.8%)
weight gain	6 (14.0%)	2 (12.5%)
weight loss	2 (4.7%)	2 (12.5%)
other	---	---
none	12 (27.9%)	7 (43.8%)

* denominator = number of female respondents

Table J.4 Frequency of symptoms reported by patients precribed gabapentin, lamotrigine and topiramate

Symptom	Number of patients (%)		
	Gabapentin (n=68)	Lamotrigine (n=18)	Topiramate (n=13)
skin			
bleeding	---	---	---
bruising	9 (13.2%)	---	---
burning sensation	2 (2.9%)	---	---
flushing	9 (13.2%)	2 (11.1%)	---
photosensitivity	5 (7.4%)	---	---
itching	8 (11.8%)	2 (11.1%)	1 (7.7%)
pale skin	---	---	1 (7.7%)
puffy skin	2 (2.9%)	---	---
pins and needles sensation	13 (19.1%)	3 (16.7%)	2 (15.4%)
skin rash	4 (5.9%)	---	---
yellowing of skin	---	---	---
other	---	---	---
none	40 (58.8%)	14 (77.8%)	8 (61.5%)
hair or nails			
change in fingernails	10 (14.7%)	1 (5.6%)	1 (7.7%)
hair loss	10 (14.7%)	11 (11.1%)	1 (7.7%)
other	---	---	---
none	48 (70.6%)	15 (83.3%)	10 (76.9%)
muscles, bone and joints			
bone or joint pain	8 (11.8%)	---	---
muscle pain	8 (11.8%)	---	---
muscle weakness	5 (7.4%)	---	---
trembling of fingers or hands	13 (19.1%)	4 (22.2%)	1 (7.7%)
unsteadiness on feet	14 (20.6%)	4 (22.2%)	3 (23.1%)
unusual body movement	4 (5.9%)	1 (5.6%)	---
other	---	---	---
none	40 (58.8%)	10 (55.6%)	10 (76.9%)
head			
headache	16 (23.5%)	2 (11.1%)	2 (15.4%)
migraine headache	5 (7.4%)	2 (11.1%)	1 (7.7%)
other	---	---	---
none	46 (67.6%)	15 (83.3%)	10 (76.9%)
vision			
blurred vision	11 (16.2%)	3 (16.7%)	1 (7.7%)
double vision	3 (4.4%)	---	---
other	---	---	---
none	50 (73.5%)	15 (83.3%)	12 (92.3%)

Symptom	Number of patients (%)		
	Gabapentin (n=68)	Lamotrigine (n=18)	Topiramate (n=13)
eyes			
itchy or irritated or inflamed eyes	8 (11.8%)	1 (5.6%)	1 (7.7%)
inability to move eyes	---	---	---
unusual movement of eyes	2 (2.9%)	1 (5.6%)	---
other	---	---	---
none	54 (79.4%)	14 (77.8%)	11 (84.6%)
hearing or ears			
change or difficulty in hearing	7 (10.3%)	4 (22.2%)	---
feeling or fullness in ears	4 (5.9%)	2 (11.1%)	---
ringing, buzzing or noises in ears	10 (14.7%)	2 (11.1%)	---
other	---	---	---
none	50 (73.5%)	13 (72.2%)	12 (92.3%)
mouth or gums			
bleeding from gums	5 (7.4%)	---	1 (7.7%)
dry mouth or throat	14 (20.6%)	1 (5.6%)	1 (7.7%)
other	3 (4.4%)	1 (5.6%)	---
none	45 (66.2%)	16 (88.9%)	11 (84.6%)
nose, throat, neck or voice			
difficulty talking	4 (5.9%)	1 (5.6%)	1 (7.7%)
slurred speech	5 (7.4%)	1 (5.6%)	1 (7.7%)
runny or stuffy nose	9 (13.2%)	---	2 (15.4%)
sore throat	4 (5.9%)	---	---
other	2 (2.9%)	---	---
none	45 (66.2%)	16 (88.9%)	9 (69.2%)
breathing or lungs			
cough	1 (1.5%)	---	---
difficulty breathing	4 (5.9%)	---	1 (7.7%)
fast breathing	2 (2.9%)	---	1 (7.7%)
slow breathing	3 (4.4%)	---	---
other	---	---	---
none	53 (77.9%)	18 (100%)	11 (84.6%)
heart or circulation			
palpitations/racing heart	11 (16.2%)	1 (5.6%)	---
missed heart beat	2 (2.9%)	---	---
other	---	---	---
none	51 (75.0%)	17 (94.4%)	12 (92.3%)

Symptom	Number of patients (%)		
	Gabapentin (n=68)	Lamotrigine (n=18)	Topiramate (n=13)
stomach or digestive system			
bloated feeling or gas	9 (13.2%)	3 (16.7%)	3 (23.1%)
decrease in appetite	3 (4.4%)	2 (11.1%)	---
indigestion or heartburn	5 (7.4%)	---	1 (7.7%)
increase in appetite	9 (13.2%)	3 (16.7%)	1 (7.7%)
pain or cramps in lower abdomen	7 (10.3%)	1 (5.6%)	---
nausea or vomiting	4 (5.9%)	---	---
vomiting blood	---	---	---
other	3 (4.4%)	---	---
none	41 (60.3%)	14 (77.8%)	8 (61.5%)
rectum or bowel movements			
black tarry stool	2 (2.9%)	---	---
constipation	13 (19.1%)	2 (11.1%)	1 (7.7%)
diarrhoea	10 (14.7%)	---	2 (15.4%)
other	---	---	---
none	44 (64.7%)	16 (88.9%)	9 (69.2%)
kidneys, bladder or urinary system			
burning while passing water	2 (2.9%)	---	---
dark brown urine	8 (11.8%)	---	1 (7.7%)
difficult in passing urine	4 (5.9%)	---	---
passing water less often	1 (1.5%)	---	---
passing water more often	11 (16.2%)	3 (16.7%)	---
bloody urine	---	---	---
other	---	---	---
none	47 (69.1%)	15 (83.3%)	11 (84.6%)
sexual function			
decrease in sexual desire	6 (8.8%)	4 (22.2%)	---
decrease in sexual ability	4 (5.9%)	1 (5.6%)	---
increase in sexual desire	2 (2.9%)	---	---
other	1 (1.5%)	---	---
none	32 (47.1%)	13 (72.2%)	7 (53.8%)
does not apply	21 (30.9%)	1 (5.6%)	6 (46.2%)
sexual organ			
abnormal vaginal bleeding	1 (2.9%)*	2 (16.7%)*	---
burning or irritated penis	---	---	1(16.7%)**
other	---	---	---
none	59 (86.8%)	14 (77.8%)	11 (84.6%)

Symptom	Number of patients (%)		
	Gabapentin (n=68)	Lamotrigine (n=18)	Topiramate (n=13)
nervous system			
confusion or delirium	4 (5.9%)	3 (16.7%)	---
light-headed or hypotension	14 (20.6%)	5 (27.8%)	1 (7.7%)
dizziness or staggering	14 (20.6%)	4 (22.2%)	2 (15.4%)
increase in convulsion	7 (10.3%)	1 (5.6%)	---
other	---	---	---
none	39 (57.4%)	10 (55.6%)	10 (76.9%)
mental health			
anxiety(nervousness)or agitation	17 (25.0%)	1 (5.6%)	1 (7.7%)
change in mood	17 (25.0%)	4 (22.2%)	1 (7.7%)
difficulty concentrating or learning	17 (25.0%)	6 (33.3%)	3 (23.1%)
hallucinations	4 (5.9%)	---	---
nightmares	---	---	1 (7.7%)
anger	13 (19.1%)	3 (16.7%)	1 (7.7%)
loss of memory	21 (30.9%)	8 (44.4%)	2 (15.4%)
thought of suicide	2 (2.9%)	---	---
reduction in sleeping	8 (11.8%)	4 (22.2%)	---
increase sleep or drowsiness	16 (23.5%)	3 (16.7%)	2 (15.4%)
other	---	---	---
none	27 (39.7%)	7 (38.9%)	5 (38.5%)
other ADRs			
increase sensitivity to cold	4 (5.9%)	2 (11.1%)	1 (7.7%)
excessive thirst	5 (7.4%)	---	2 (15.4%)
fever	---	---	---
flu-like symptoms	---	---	---
increase sweating	13 (19.1%)	2 (11.1%)	2 (15.4%)
unusual tiredness or weakness	13 (19.1%)	3 (16.7%)	2 (15.4%)
weight gain	24 (35.3%)	4 (22.2%)	1 (7.7%)
weight loss	1 (1.5%)	---	3 (23.1%)
other	---	---	---
none	30 (44.1%)	10 (55.6%)	6 (46.2%)

* denominator = number of female respondents
** denominator = number of male respondents